STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 125478

TO: Ralph J Gitomer
Location: 3e65 / 3e71
Tuesday, July 06, 2004
Art Unit: 1651
Phone: 272-0916
Serial Number: 10 / 716578

From: Jan Delaval
Location: Biotech-Chem Library
Rem 1A51
Phone: 272-2504

jan.delaval@uspto.gov

Search Notes

STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 126433

TO: Ralph J Gitomer Location: 3d65 / 3e71 Tuesday, July 06, 2004 Art Unit: 1651 Phone: 272-0916 Serial Number: 10 / 716578	From: Jan Delaval Location: Biotech-Chem Library Rem 1A51 Phone: 272-2504 jan.delaval@uspto.gov

Search Notes

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=> fil reg
FILE 'REGISTRY' ENTERED AT 08:41:20 ON 06 JUL 2004
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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:     5 JUL 2004  HIGHEST RN 704870-92-8
DICTIONARY FILE UPDATES:    5 JUL 2004  HIGHEST RN 704870-92-8

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d sta que l92
L88        35103 SEA FILE=REGISTRY ABB=ON  PLU=ON  4432.3.5/RID
L89              STR

O---CH2---CH2
1   2    3


NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS   3

STEREO ATTRIBUTES: NONE
L90         4765 SEA FILE=REGISTRY SUB=L88 SSS FUL L89
L91          102 SEA FILE=REGISTRY ABB=ON  PLU=ON  L88 AND C2H4O
L92         4772 SEA FILE=REGISTRY ABB=ON  PLU=ON  (L90 OR L91)


=> d sta que l96
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L89              STR

O---CH2---CH2
1   2    3


NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS   3

STEREO ATTRIBUTES: NONE
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L91          102 SEA FILE=REGISTRY ABB=ON  PLU=ON  L88 AND C2H4O
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L92          4772 SEA FILE=REGISTRY ABB=ON  PLU=ON  (L90 OR L91)
L95               STR
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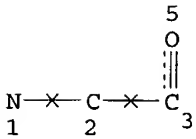


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DEFAULT ECLEVEL IS LIMITED

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STEREO ATTRIBUTES: NONE
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100.0% PROCESSED   1176 ITERATIONS                      133 ANSWERS
SEARCH TIME: 00.00.01


=> d his

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               SET COST OFF

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L2            59 S E3-E7
               E NNOCHIRI/AU
               E NOCHIRI/AU
               E NKEM/AU
               E RADHAKRISHNAN B/AU
L3            54 S E3,E7,E8
               E PRICE C/AU
L4           120 S E3,E10,E11
               E PRICE CHRIS/AU
L5            35 S E5,E13,E14
               E ANDERSON W/AU
L6           134 S E3
L7            67 S E47-E49
L8            35 S E120,E123-E125
               E ANSARI A/AU
L9           100 S E3,E13-E15
               E ANSARI ASLAM/AU
L10           11 S E5
               E PROTEIN DELIVERY/PA,CS
L11           12 S E5-E10
               E NOBEX/PA,CS
L12           37 S E3-E16
L13      1114220 S PEPTIDE#/CW OR PROTEIN#/CW
L14       116058 S (PEPTIDE# OR PROTEIN# OR AMINO()ACID#)/SC,SX
L15      2008395 S ?PEPTIDE OR ?PROTEIN

     FILE 'REGISTRY' ENTERED AT 07:29:53 ON 06 JUL 2004

     FILE 'HCAPLUS' ENTERED AT 07:34:05 ON 06 JUL 2004
L16           387 S ARGININE()(DEAMINASE OR DEAMINEASE OR DEIMINASE)
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L17          22 S 50-56-6 OR 1407-47-2 OR 9000-96-8 OR 9001-73-4 OR 9001-78-9 O
L18          10 S 17650-98-5 OR 39379-15-2 OR 51110-01-1 OR 52906-92-0 OR 60118
                E BLOOD-CLOT/CN
L19           2 S BLOOD-COAGULATING?/CN
L20        1434 S BLOOD-COAGULATION?/CN
                E ENKEPHALIN
L21         281 S E3
L22           1 S 58569-55-4

     FILE 'HCAPLUS' ENTERED AT 07:43:13 ON 06 JUL 2004
L23      289909 S L17,L18
L24      397789 S L19,L20,L21
L25        5565 S L22
L26        3914 S (MET OR MET5 OR MET 5)() ENKEPHALIN#
L27          68 S 1 5 ADRENORPHIN
L28        3645 S METHIONIN# ENKEPHALIN
L29          65 S METHIONINEENKEPHALIN OR  OPIOID GROWTH FACTOR
L30        7026 S L25-L29
                E ENKEPHALIN/CT
L31       12916 S E9+OLD,NT,PFT
L32      132866 S ANTIBODIES/CT
                E BLOOD-COAGULATION/CT
L33       33727 S E28+OLD,NT,PFT
                E CD4/CT
L34        7913 S E4+OLD,NT,PFT
                E HEMOGLOBIN/CT
L35       56767 S E3+OLD,NT,PFT OR E20+OLD,NT,PFT
                E HYPOTHALM/CT
L36           6 S E4
                E E4+ALL
L37          13 S HYPOTHALMIC(L)RELEASING(L)FACTOR
                E INTEFERON/CT
                E INTERFERON/CT
L38       61823 S E3+OLD,NT,PFT OR E85+OLD,NT,PFT
                E OPIODS/CT
                E OPIOIDS/CT
L39       28884 S E3+OLD,NT,PFT
                E OPIOID RECEPTOR/CT
L40       20483 S E8+OLD,NT,PFT
L41      523908 S ENKEPHALIN OR ADRENOCORTICOTROPIC(S)HORMONE OR L16 OR RIBONUC
L42      296784 S ENDORPHIN OR ERYTHROPOIETI OR EPO OR GASTRIN RELEASING PEPTID
L43      250134 S PROLACTIN OR CD4 OR CD 4 OR SOMATOMEDIN OR SOMATOSTATIN OR SO
L44       63842 S L13-L16,L23-L24,L31-L43 AND ?CONJUGAT?
L45          69 S L30 AND ?CONJUGAT?
L46        5689 S L44 AND ?OLIGO?
L47           6 S L45 AND ?OLIGO?
L48         469 S L46 AND (LIPOPHIL? OR FATTY ACID OR ALKYL OR CHOLESTEROL)

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L49           1 S CHOLESTEROL/CN

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L50         108 S L49 AND L46
L51           3 S L45 AND (LIPOPHIL? OR FATTY ACID OR ALKYL OR CHOLESTEROL OR L
L52        5383 S L44 AND (HYDROPHIL? OR SUGAR OR PEG OR POLYETHYLENEGLYCOL OR
L53         927 S L46,L48,L50 AND L52
L54          69 S L45,L47,L51
L55         408 S (ERYTHROPOIETIN OR CHOLECYSTOKININ OR L16) AND ?CONJUGAT?
L56          59 S L55 AND ?OLIGO?
L57          35 S L55 AND (LIPOPHIL? OR FATTY ACID OR ALKYL OR CHOLESTEROL OR L
L58          22 S L56 AND (HYDROPHIL? OR SUGAR OR PEG OR POLYETHYLENEGLYCOL OR
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L59          989 S L56-L58,L53
L60            2 S L59 AND L54
L61            1 S L54,L60 AND L1-L12
                 E AUSARI A/AU
L62            1 S E4,L61
L63            1 S L60 NOT L62
L64            2 S L60-L63
L65            1 S ADENOSINE DEAMINASE AND L64
L66            2 S L64,L65
L67          590 S L2-L12
L68           94 S L67 AND (L13-L15,L23-L43 OR ERYTHROPOIETIN OR CHOLECYSTOKININ
L69           27 S L68 AND ?CONJUGAT?
L70           21 S L69 AND ?OLIGO?
L71           10 S L69 AND AMPHIPHIL?
L72            8 S L69 AND LIPOPHIL?
L73            7 S L69 AND HYDROPHIL?
L74           17 S L71-L73
L75           12 S L74 AND ?OLIGO?
L76            5 S L74 NOT L75
L77           18 S L75,L76,L66
L78           10 S L69 NOT L77
L79            9 S L78 AND ?OLIGO?
L80           27 S L77,L79
L81           22 S L80 AND ?OLIGO?
L82           27 S L80 AND ?CONJUGAT?
L83           27 S L80-L82
                 SEL RN L1

     FILE 'REGISTRY' ENTERED AT 08:19:26 ON 06 JUL 2004
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L85           25 S L84 NOT L17-L22,L49
L86            6 S L85 AND SQL/FA

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L87            1 S L86

     FILE 'REGISTRY' ENTERED AT 08:20:58 ON 06 JUL 2004
                 E 4432.3.5/RID
L88        35103 S E3
L89                STR
L90         4765 S L89 FUL SUB=L88
                 SAV L90 GITOMER716/A
L91          102 S L88 AND C2H4O
L92         4772 S L90,L91
L93           11 S L92 AND SQL/FA
L94            3 S L93 NOT NUCLEIC?/FS
L95                STR
L96          133 S L95 FUL SUB=L92
                 SAV L96 GITOMER716A/A
L97            3 S L96 AND SQL/FA
L98            3 S L94,L97
L99          130 S L96 NOT L98
L100           3 S L99 AND (C37H60N2O6 OR C37H62N2O7 OR C31H54N2O2)
L101           2 S L98 NOT MXS/CI
L102          10 S L86,L100,L101

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L103           5 S L102
L104           1 S L103 AND L1-L12
L105          31 S L83,L87,L103,L104
L106           5 S L105 NOT L1-L12
L107          26 S L105 NOT L106
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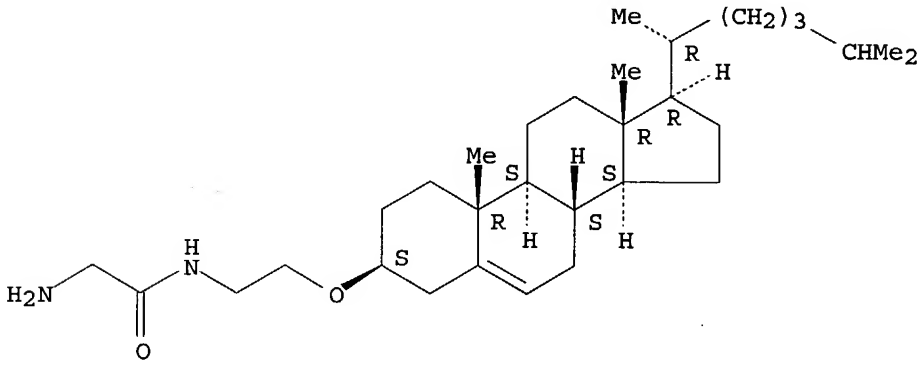
FILE 'REGISTRY' ENTERED AT 08:41:20 ON 06 JUL 2004

=> d ide can tot l102

L102 ANSWER 1 OF 10 REGISTRY COPYRIGHT 2004 ACS on STN
RN 671792-75-9 REGISTRY
CN Acetamide, 2-amino-N-[2-[(3β)-cholest-5-en-3-yloxy]ethyl]-, monohydrochloride (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF **C31 H54 N2 O2 . Cl H**
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PRP (Properties)

Absolute stereochemistry.



"aminated" glycine + 1 x PEG + cholesterol

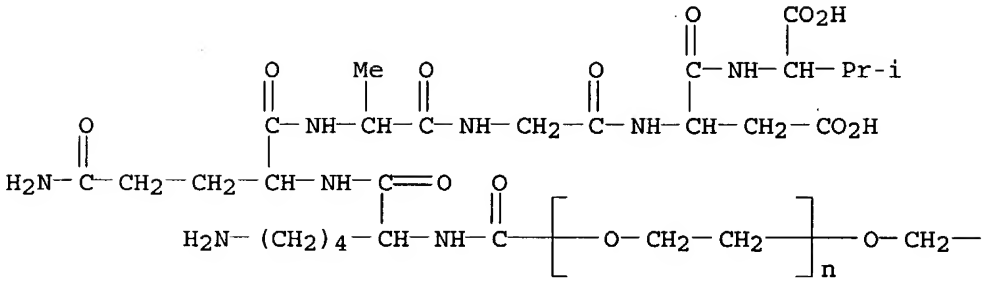
CA (1907 TO DATE)
CAPLUS (1907 TO DATE)

GHT 2004 ACS on STN

o-ω-[2-[[[(3β)-cholest-5-
]-, 1-ester with N2-carboxy-L-lysyl-L-spartyl-L-valine (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE
DR 497861-56-0
MF **(C2 H4 O)n C56 H93 N9 O14**
CI PMS
PCT Polyether
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)

RELATED SEQUENCES AVAILABLE WITH SEQLINK

PAGE 1-A



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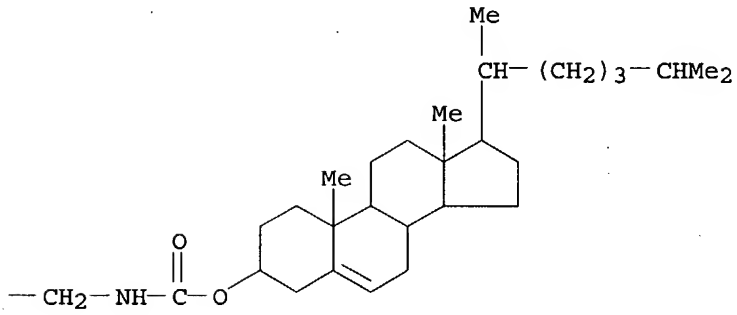


2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 138:193258

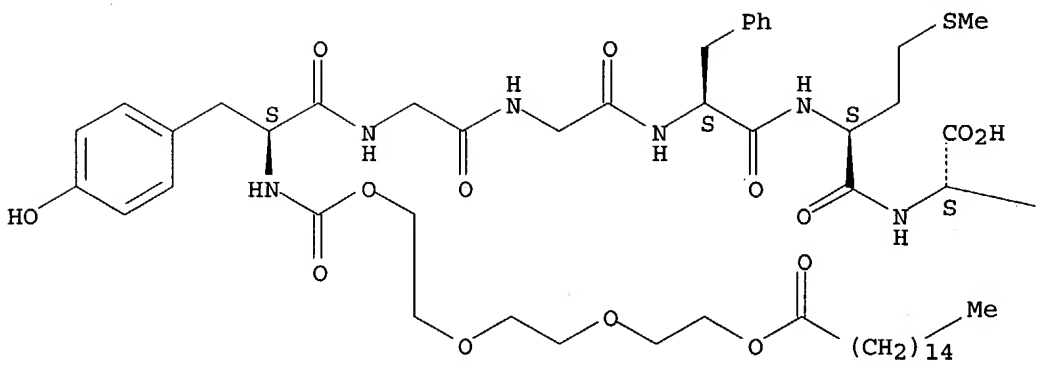
REFERENCE 2: 133:182966

L102 ANSWER 3 OF 10 REGISTRY COPYRIGHT 2004 ACS on STN
RN **259229-08-8** REGISTRY
CN L-Lysine, N-(1,12-dioxo-2,5,8,11-tetraoxaheptacos-1-yl)-L-tyrosylglycylglycyl-L-phenylalanyl-L-methionyl-N6-(1,12-dioxo-2,5,8,11-tetraoxaheptacos-1-yl)- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C79 H131 N7 O20 S
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); USES (Uses)

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A



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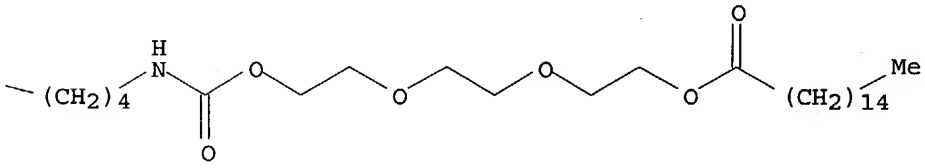


1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

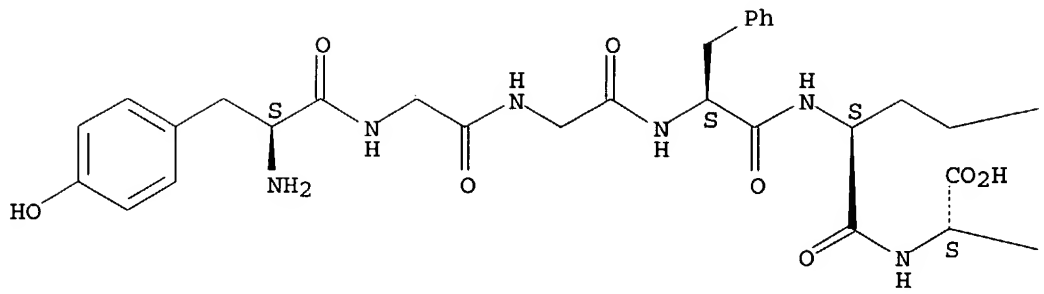
REFERENCE 1: 132:185416

L102 ANSWER 4 OF 10 REGISTRY COPYRIGHT 2004 ACS on STN
RN **259229-07-7** REGISTRY
CN L-Lysine, L-tyrosylglycylglycyl-L-phenylalanyl-L-methionyl-N6-(1,12-dioxo-2,5,8,11-tetraoxaheptacos-1-yl)- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C56 H89 N7 O14 S
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); USES (Uses)

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A



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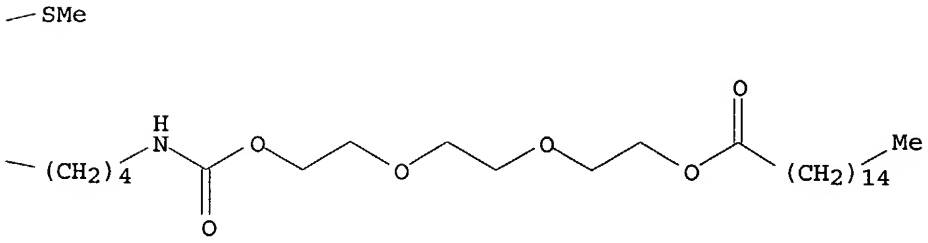


1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

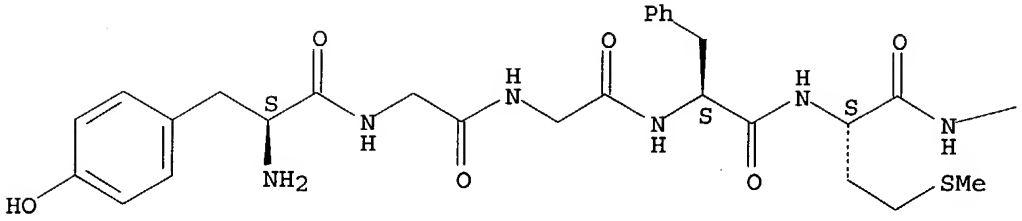
REFERENCE 1: 132:185416

L102 ANSWER 5 OF 10 REGISTRY COPYRIGHT 2004 ACS on STN
RN **259229-06-6** REGISTRY
CN L-Lysine, L-tyrosylglycylglycyl-L-phenylalanyl-L-methionyl-N6-[[2-[2-[2-[(3β)-cholest-5-en-3-yloxy]-2-oxoethoxy]ethoxy]ethoxy]carbonyl]- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C67 H101 N7 O14 S
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); USES (Uses)

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A



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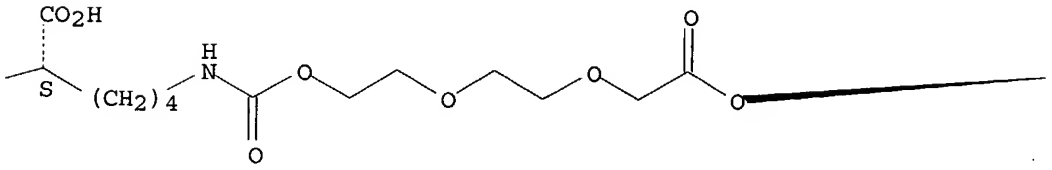

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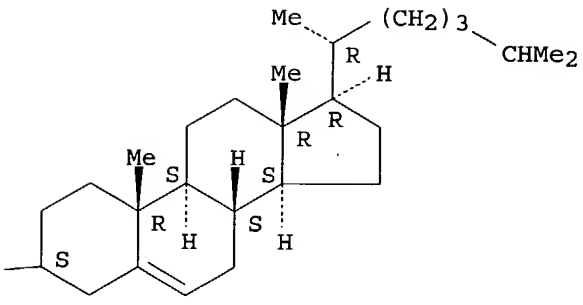


1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 132:185416

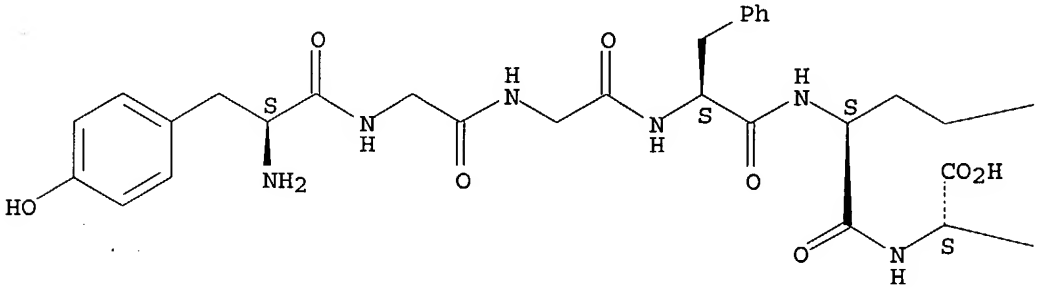
L102 ANSWER 6 OF 10 REGISTRY COPYRIGHT 2004 ACS on STN
RN **259229-05-5** REGISTRY
CN L-Lysine, L-tyrosylglycylglycyl-L-phenylalanyl-L-methionyl-N6-[[2-[2-(hexadecyloxy)ethoxy]ethoxy]carbonyl]- (9CI) (CA INDEX NAME)

FS PROTEIN SEQUENCE; STEREOSEARCH
MF C54 H87 N7 O12 S
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); USES (Uses)

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A



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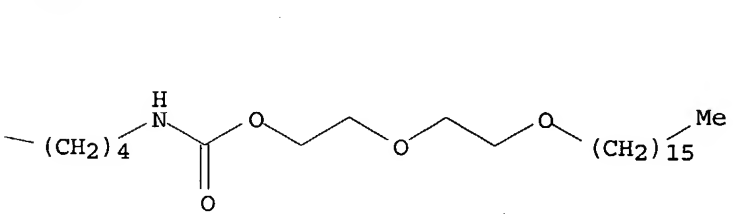

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 132:185416

L102 ANSWER 7 OF 10 REGISTRY COPYRIGHT 2004 ACS on STN
RN **259229-04-4** REGISTRY
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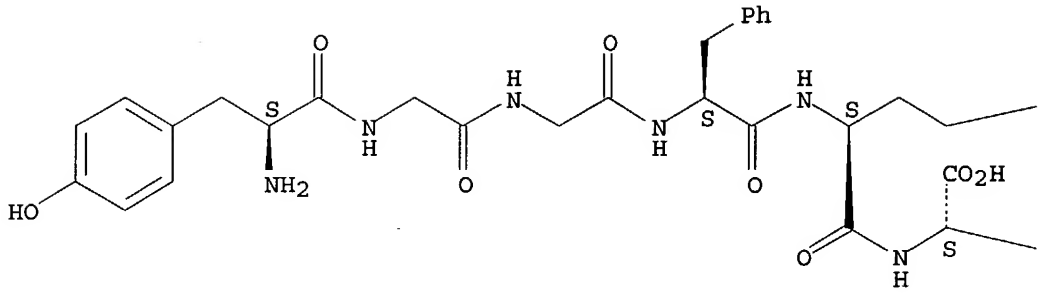
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C56 H84 N8 O12 S
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); USES (Uses)

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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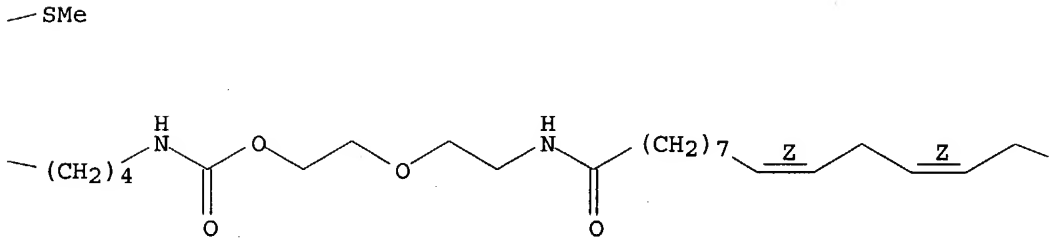

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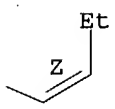

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 132:185416

L102 ANSWER 8 OF 10 REGISTRY COPYRIGHT 2004 ACS on STN
RN **259229-03-3** REGISTRY
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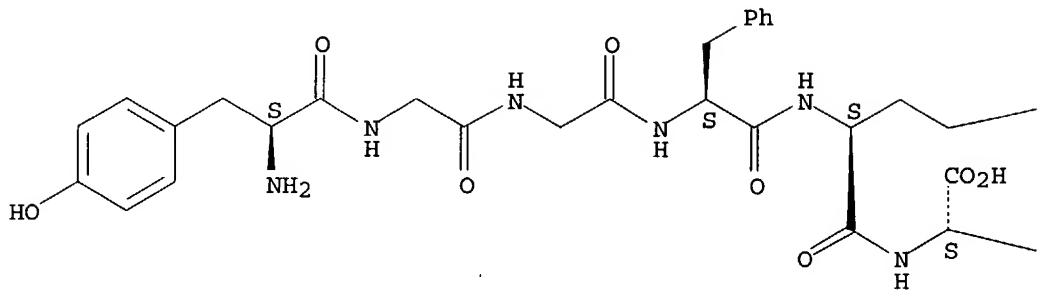
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C60 H86 N8 O12 S
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); USES (Uses)

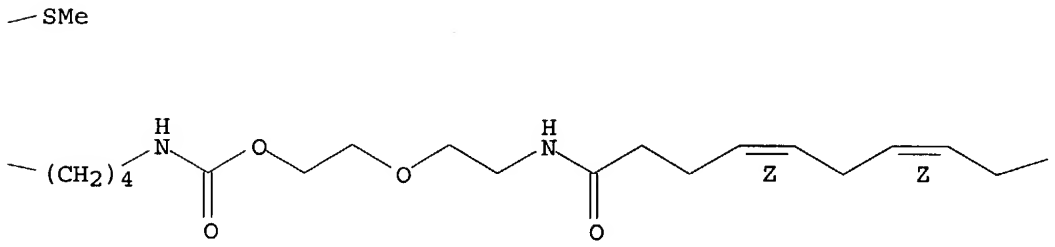
RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



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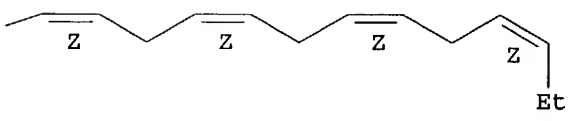


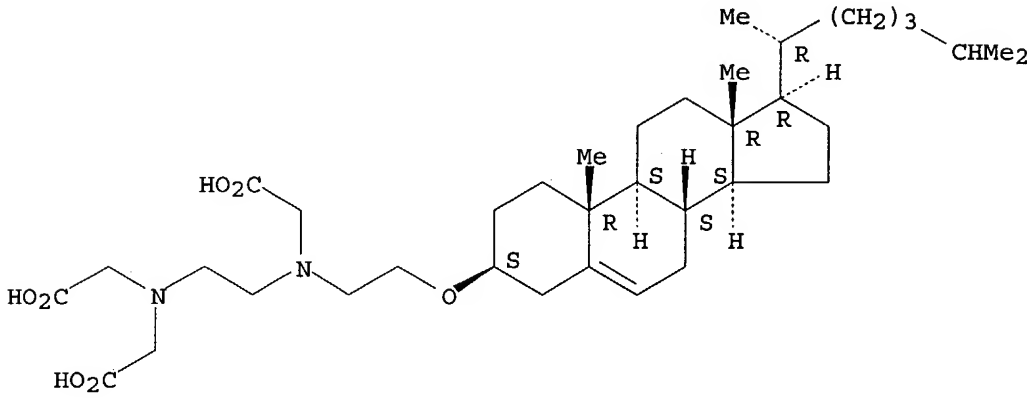
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 132:185416

L102 ANSWER 9 OF 10 REGISTRY COPYRIGHT 2004 ACS on STN
RN 77975-62-3 REGISTRY
CN Glycine, N-[2-[bis(carboxymethyl)amino]ethyl]-N-[2-[[(3β)-cholest-5-en-3-yl]oxy]ethyl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:

CN Cholestane, glycine deriv
FS STEREOSEARCH
MF **C37 H62 N2 O7**
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: PREP (Preparation); RACT (Reactant or reagent)

Absolute stereochemistry.



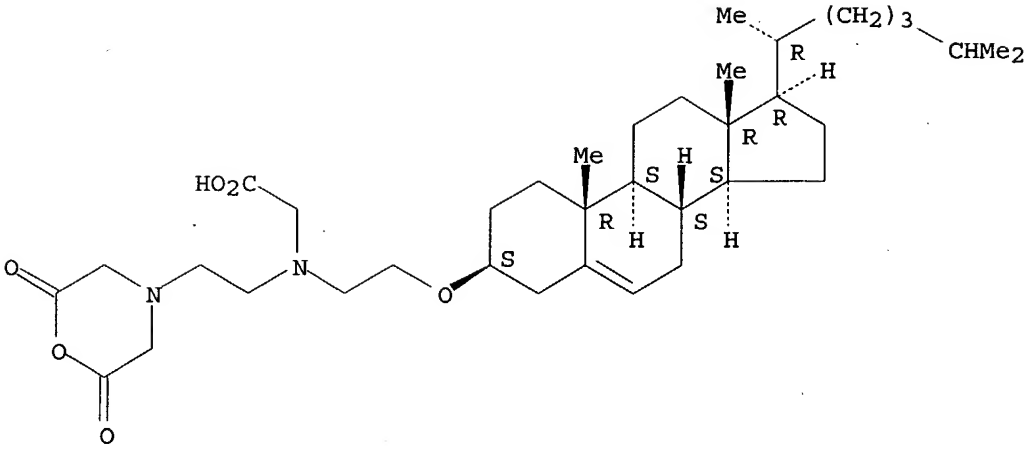
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 95:38681

L102 ANSWER 10 OF 10 REGISTRY COPYRIGHT 2004 ACS on STN
RN 77975-61-2 REGISTRY
CN Glycine, N-[[[(3β)-cholest-5-en-3-yl]oxy]ethyl]-N-[2-(2,6-dioxo-4-morpholinyl)ethyl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Cholestane, glycine deriv
FS STEREOSEARCH
MF **C37 H60 N2 O6**
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: PREP (Preparation); RACT (Reactant or reagent)

Absolute stereochemistry.



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1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 95:38681

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FILE 'HCAPLUS' ENTERED AT 08:42:48 ON 06 JUL 2004
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FILE COVERS 1907 - 6 Jul 2004 VOL 141 ISS 2
FILE LAST UPDATED: 5 Jul 2004 (20040705/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

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L106 ANSWER 1 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2004:8780 HCAPLUS
DN 140:248983
ED Entered STN: 07 Jan 2004
TI Single additional methylene group in the head-group region imparts high gene transfer efficacy to a transfection-incompetent cationic lipid
AU Singh, Rajkumar Sunil; Chaudhuri, Arabinda
CS Division of Lipid Science and Technology, Indian Institute of Chemical Technology, Hyderabad, 500 007, India

SO FEBS Letters (2003), Volume Date 2004, 556(1-3), 86-90
CODEN: FEBLAL; ISSN: 0014-5793
PB Elsevier Science B.V.
DT Journal
LA English
CC 6-6 (General Biochemistry)
Section cross-reference(s): 1, 3
AB In combination with equimolar 1,2-dioleoyl-L-α-glycero-3-phosphatidyl ethanolamine, a novel cholesterol-based cationic lipid with β-alanine head-group (2) has been demonstrated to be strikingly more efficacious (10-24-fold) in transfecting CHO, COS-1 and HepG2 cells than its glycine analog (1) containing just one less methylene unit in its head-group region. Syntheses, characterizations and in vitro transfection biol. of lipids 1 and 2 are described. Present findings demonstrate that even truly minor structural alterations, such as inclusion of just one addnl. methylene functionality in the polar head-group region, can convert an essentially transfection-incompetent cholesterol-based cationic amphiphile to a remarkably efficient cationic transfection lipid.
ST methylene group gene transfer transfection cation lipid
IT Human
Methylene group
Transformation, genetic
(single addnl. methylene group in head-group region imparts high gene transfer efficacy to transfection-incompetent cationic lipid)
IT DNA
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(single addnl. methylene group in head-group region imparts high gene transfer efficacy to transfection-incompetent cationic lipid)
IT 4004-05-1 137056-72-5, DC-Chol
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(single addnl. methylene group in head-group region imparts high gene transfer efficacy to transfection-incompetent cationic lipid)
IT **671792-75-9P** 671792-76-0P
RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(single addnl. methylene group in head-group region imparts high gene transfer efficacy to transfection-incompetent cationic lipid)
IT 3303-84-2 151392-05-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(single addnl. methylene group in head-group region imparts high gene transfer efficacy to transfection-incompetent cationic lipid)
IT 671792-74-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(single addnl. methylene group in head-group region imparts high gene transfer efficacy to transfection-incompetent cationic lipid)
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
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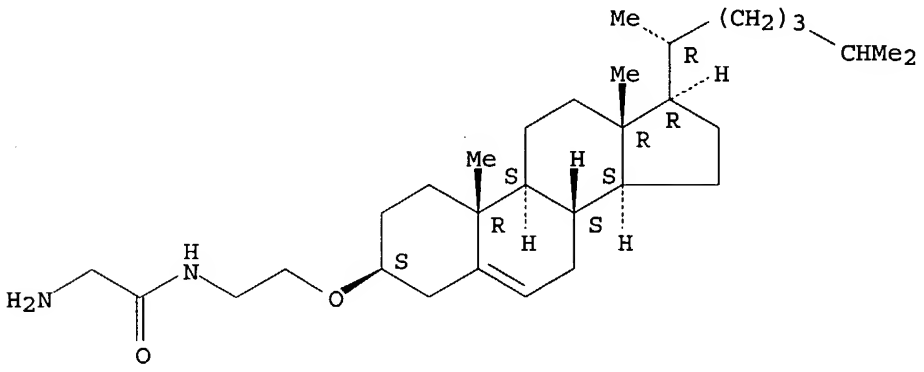
IT **671792-75-9P**
RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(single addnl. methylene group in head-group region imparts high gene transfer efficacy to transfection-incompetent cationic lipid)
RN 671792-75-9 HCAPLUS
CN Acetamide, 2-amino-N-[2-[(3β)-cholest-5-en-3-yloxy]ethyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

L106 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:129325 HCAPLUS
DN 138:193258
ED Entered STN: 20 Feb 2003
TI Methods of imaging and treatment with targeted compositions
IN Unger, Evan C.; Wu, Yunqiu
PA Bristol-Myers Squibb Medical Imaging, Inc., USA
SO U.S., 96 pp., Cont.-in-part of U.S. Ser. No. 218,660.
CODEN: USXXAM
DT Patent
LA English
IC ICM A61B008-00
ICS A61R009-127; A61R038-00; A61R038-04
NCL 424009520; 424009510; 424009520; 424009500; 424450000; 600431000; 600437000; 514018000; 514002000
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 14, 37

FAN.CNT 8

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6521211	B1	20030218	US 1999-243640	19990203
	CN 1187137	A	19980708	CN 1996-194499	19960606
	CN 1083280	B	20020424		
	WO 2000045856	A2	20000810	WO 2000-US2620	20000202
	WO 2000045856	A3	20010215		
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	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 1146911	A2	20011024	EP 2000-914480	20000202
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	US 2003157025	A1	20030821	US 2003-341167	20030113
PRAI	US 1995-497684	B2	19950607		
	US 1996-640464	B2	19960501		
	US 1996-660032	B2	19960606		
	US 1998-73913P	P	19980206		
	US 1998-218660	A2	19981222		
	US 1999-243640	A	19990203		
	WO 2000-US2620	W	20000202		

AB The invention concerns novel ultrasound methods comprising administering to a patient a targeted vesicle composition which comprises vesicles comprising a lipid, protein or polymer, encapsulating a gas, in combination with a targeting ligand, and scanning the patient using ultrasound. The scanning may comprise exposing the patient to a first type of ultrasound energy and then interrogating the patient using a second type of ultrasound energy. The targeting ligand preferably targets tissues, cells or receptors, including myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein GPIIbIIIa receptor. The methods may be used to detect a thrombus, enhancement of an old or echogenic thrombus, low concns. of vesicles and vesicles targeted to tissues, cells or receptors.

ST liposome ultrasound imaging treatment thrombus diagnosis

IT Steroids, analysis
RL: ANT (Analyte); ANST (Analytical study)
(analogs; methods of imaging and treatment with targeted compns.)

IT Bond
(covalent; methods of imaging and treatment with targeted compns.)

IT Blood vessel
(endothelium; methods of imaging and treatment with targeted compns.)

IT Perfluorocarbons
RL: NUU (Other use, unclassified); PRP (Properties); USES (Uses)
(gas; methods of imaging and treatment with targeted compns.)

IT Polymers, uses
RL: NUU (Other use, unclassified); PRP (Properties); USES (Uses)
(hydrophilic; methods of imaging and treatment with targeted compns.)

IT Drug delivery systems
(liposomes; methods of imaging and treatment with targeted compns.)

IT Diagnosis
Encapsulation
Epithelium
Human
Neoplasm
Sound and Ultrasound
Thrombus
(methods of imaging and treatment with targeted compns.)

IT Oligosaccharides, analysis
Peptides, analysis
Proteins
Steroids, analysis
RL: ANT (Analyte); ANST (Analytical study)
(methods of imaging and treatment with targeted compns.)

IT Integrins
RL: ANT (Analyte); DGN (Diagnostic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(methods of imaging and treatment with targeted compns.)

IT Phosphatidic acids
RL: NUU (Other use, unclassified); USES (Uses)
(methods of imaging and treatment with targeted compns.)

IT Polyoxyalkylenes, uses
Polyphosphazenes
RL: NUU (Other use, unclassified); PRP (Properties); USES (Uses)
(methods of imaging and treatment with targeted compns.)

IT Integrins
RL: ANT (Analyte); DGN (Diagnostic use); PRP (Properties); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(αIIbβ3; methods of imaging and treatment with targeted compns.)

IT 80755-87-9 99896-85-2
RL: ANT (Analyte); ANST (Analytical study)
(amino acid sequence; methods of imaging and treatment with targeted compns.)

IT 76-19-7, Perfluoropropane 355-25-9, Perfluorobutane 7782-41-4, Fluorine, uses
RL: NUU (Other use, unclassified); PRP (Properties); USES (Uses)
(gas; methods of imaging and treatment with targeted compns.)

IT 186750-17-4P 186750-21-0P
RL: ARG (Analytical reagent use); RCT (Reactant); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(methods of imaging and treatment with targeted compns.)

IT 186750-11-8P 186750-14-1P 186750-26-5P 186750-28-7P 186750-29-8P
186750-31-2P 221553-44-2DP, conjugate with protein A 221553-48-6P
287952-89-0P 287952-92-5P 287952-93-6P 287952-95-8P
287952-99-2P 497861-50-4P 497861-51-5P 497861-52-6P
497861-53-7DP, conjugate with protein A 497861-54-8P 497861-55-9P
RL: ARG (Analytical reagent use); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); USES (Uses)
(methods of imaging and treatment with targeted compns.)

IT 63-89-8, Dipalmitoylphosphatidylcholine 816-94-4, Distearoylphosphatidylcholine 923-61-5 4004-05-1, Dioleoylphosphatidylethanolamine 18194-24-6, Dimyristoylphosphatidylcholine 25322-68-3, Polyethylene glycol
497861-47-9 497861-48-0
RL: NUU (Other use, unclassified); USES (Uses)
(methods of imaging and treatment with targeted compns.)

IT 9002-89-5, Polyvinyl alcohol 9003-05-8 9003-39-8, Polyvinylpyrrolidone
25014-12-4, Polymethacrylamide 408512-66-3
RL: NUU (Other use, unclassified); PRP (Properties); USES (Uses)
(methods of imaging and treatment with targeted compns.)

IT 39927-08-7DP, cyclic anhydride derivs. 55750-62-4P 56309-86-5P
186750-12-9P 186750-13-0P 186750-15-2P 186750-18-5P 186750-19-6P
186750-20-9P 186750-22-1P 186750-23-2P 186750-25-4P 186750-27-6P
287952-86-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(methods of imaging and treatment with targeted compns.)

IT 498593-56-9 498593-57-0 498593-58-1 498593-59-2 498593-60-5
498593-61-6 498593-62-7

RL: PRP (Properties)
(unclaimed protein sequence; methods of imaging and treatment with targeted compns.)

IT 67869-62-9 91037-65-9 91037-75-1 132634-52-7 177597-41-0
288067-16-3 379270-65-2 498527-63-2 498527-64-3 498527-65-4
498527-66-5 498527-67-6 498527-68-7 498527-69-8
RL: PRP (Properties)
(unclaimed sequence; methods of imaging and treatment with targeted compns.)

RE.CNT 546 THERE ARE 546 CITED REFERENCES AVAILABLE FOR THIS RECORD

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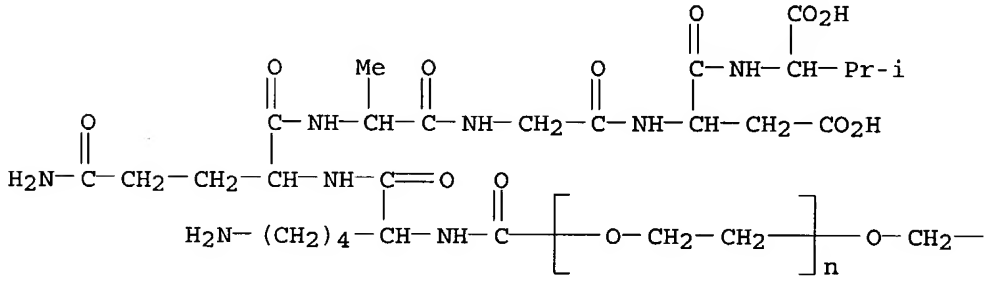
(544) Zarif, L; Artificial Cells, Blood Substitutes, and Immobilization Biotechnology 1994, V22(4), P1193 HCAPLUS
(545) Zarif, L; JAOCS 1989, V66(10), P1515 HCAPLUS
(546) Zhou; J Control Release 1992, V19, P269 HCAPLUS

IT **287952-99-2P**
RL: ARG (Analytical reagent use); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); USES (Uses)
(methods of imaging and treatment with targeted compns.)

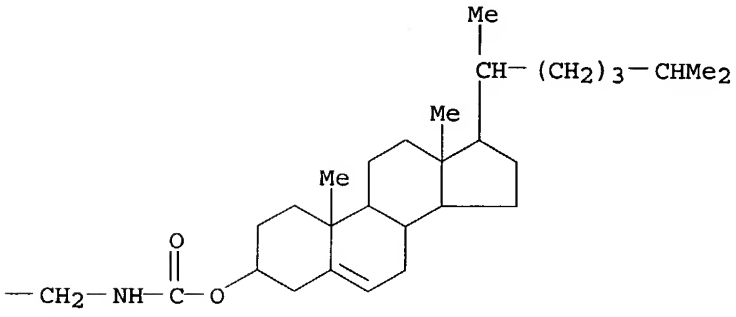
RN 287952-99-2 HCAPLUS

CN Poly(oxy-1,2-ethanediyl), α-hydro-ω-[2-[[[(3β)-cholest-5-en-3-yloxy]carbonyl]amino]ethoxy]-, 1-ester with N2-carboxy-L-lysyl-L-glutaminyl-L-alanylglycyl-L-α-aspartyl-L-valine (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B



L106 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:553450 HCAPLUS
DN 133:182966
ED Entered STN: 11 Aug 2000
TI Novel methods of imaging and treatment with targeted compositions
IN Ungr, Evan C.; Wu, Yunqiu

PA ImaRx Pharmaceutical Corp., USA
SO PCT Int. Appl., 211 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K049-00
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 8, 23
FAN.CNT 8

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000045856	A2	20000810	WO 2000-US2620	20000202
	WO 2000045856	A3	20010215		
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 6521211	B1	20030218	US 1999-243640	19990203
	EP 1146911	A2	20011024	EP 2000-914480	20000202
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
PRAI	US 1999-243640	A	19990203		
	US 1995-497684	B2	19950607		
	US 1996-640464	B2	19960501		
	US 1996-660032	B2	19960606		
	US 1998-73913P	P	19980206		
	US 1998-218660	A2	19981222		
	WO 2000-US2620	W	20000202		

AB Novel ultrasound methods comprising administering to a patient a targeted vesicle composition which comprises vesicles comprising a lipid, protein or polymer, encapsulating a gas, in combination with a targeting ligand, and scanning the patient using ultrasound. The scanning may comprise exposing the patient to a first type of ultrasound energy and then interrogating the patient using a second type of ultrasound energy. The targeting ligand preferably targets tissues, cells or receptors, including myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein GPIIbIIIa receptor. The methods may be used to detect a thrombus, enhancement of an old or echo genic thrombus low concns. of vesicles and vesicles targeted to tissues, cells or receptors.

ST liposome micelle ultrasound imaging treatment
IT Proteins, specific or class
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(A, conjugates, with PEGylated phospholipids; ultrasound imaging and treatment with targeted compns.)
IT Imaging agents
(acoustic imaging contrast agents; ultrasound imaging and treatment with targeted compns.)
IT Imaging
Imaging agents
(acoustic; ultrasound imaging and treatment with targeted compns.)
IT Polyoxyalkylenes, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(aminated amidated end groups; ultrasound imaging and treatment with targeted compns.)
IT Polyoxyalkylenes, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(aminocarboxy and triethylamine salt derivs.; ultrasound imaging and

treatment with targeted compns.)
IT Polyoxyalkylenes, preparation
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(aminocarboxy terminated; ultrasound imaging and treatment with targeted compns.)
IT Polyesters, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(caprolactone-based; ultrasound imaging and treatment with targeted compns.)
IT Antibodies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(conjugates, maleimidophenylbutyrate; ultrasound imaging and treatment with targeted compns.)
IT Artery
(coronary, angioplasty; ultrasound imaging and treatment with targeted compns.)
IT Artery, disease
(coronary; ultrasound imaging and treatment with targeted compns.)
IT Blood vessel
(endothelium; ultrasound imaging and treatment with targeted compns.)
IT Polyoxyalkylenes, biological studies
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(fluorinated stearoylphosphatidylethanolamine and peptide end groups; ultrasound imaging and treatment with targeted compns.)
IT Polyoxyalkylenes, preparation
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(fluorinated stearoylphosphatidylethanolamine end groups; ultrasound imaging and treatment with targeted compns.)
IT Polyesters, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lactic acid-based; ultrasound imaging and treatment with targeted compns.)
IT Heart, disease
(left ventricle; ultrasound imaging and treatment with targeted compns.)
IT Drug delivery systems
(liposomes; ultrasound imaging and treatment with targeted compns.)
IT Antibodies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(monoclonal; ultrasound imaging and treatment with targeted compns.)
IT Heart
(myocyte; ultrasound imaging and treatment with targeted compns.)
IT Pancreas, neoplasm
(neuroendocrine; ultrasound imaging and treatment with targeted compns.)
IT Plasmid vectors
(pSVβ-gal; ultrasound imaging and treatment with targeted compns.)
IT Albumins, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(serum; ultrasound imaging and treatment with targeted compns.)
IT Polyoxyalkylenes, biological studies
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(stearoylphosphatidylethanolamine, aminated and amidated end groups; ultrasound imaging and treatment with targeted compns.)
IT Polyoxyalkylenes, preparation
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(stearoylphosphatidylethanolamine, tert-butoxycarbonyl, aminated and amidated end groups; ultrasound imaging and treatment with targeted

compns.)
IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(targeting of; ultrasound imaging and treatment with targeted compns.)
IT Acoustic devices
Antitumor agents
Atherosclerosis
Crosslinking
Drug delivery systems
Drug targeting
Epithelium
Heart
Inflammation
Liver
Micelles
Neoplasm
Second sound
Sound and Ultrasound
Thrombus
Vasodilators
(ultrasound imaging and treatment with targeted compns.)
IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ultrasound imaging and treatment with targeted compns.)
IT Antibodies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ultrasound imaging and treatment with targeted compns.)
IT Epoxy resins, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ultrasound imaging and treatment with targeted compns.)
IT Ligands
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ultrasound imaging and treatment with targeted compns.)
IT Lipids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ultrasound imaging and treatment with targeted compns.)
IT Peptides, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ultrasound imaging and treatment with targeted compns.)
IT Perfluorocarbons
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ultrasound imaging and treatment with targeted compns.)
IT Phosphatidic acids
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ultrasound imaging and treatment with targeted compns.)
IT Phosphatidylcholines, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ultrasound imaging and treatment with targeted compns.)
IT Phosphatidylethanolamines, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ultrasound imaging and treatment with targeted compns.)
IT Phospholipids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ultrasound imaging and treatment with targeted compns.)
IT Polyamides, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ultrasound imaging and treatment with targeted compns.)
IT Polymers, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ultrasound imaging and treatment with targeted compns.)
IT Polyoxyalkylenes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ultrasound imaging and treatment with targeted compns.)

IT Polyoxyalkylenes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ultrasound imaging and treatment with targeted compns.)
IT Polyphosphazenes
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ultrasound imaging and treatment with targeted compns.)
IT Polysaccharides, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ultrasound imaging and treatment with targeted compns.)
IT Polysiloxanes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ultrasound imaging and treatment with targeted compns.)
IT Porphyrins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ultrasound imaging and treatment with targeted compns.)
IT Proteins, general, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ultrasound imaging and treatment with targeted compns.)
IT Steroids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ultrasound imaging and treatment with targeted compns.)
IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(αIIbβ3, targeting of; ultrasound imaging and treatment with targeted compns.)
IT 9031-11-2, β-Galactosidase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ultrasound imaging and treatment with targeted compns.)
IT 79481-27-9P 79605-84-8P 287952-92-5P 287952-93-6P 287952-95-8P
287952-97-0P **287952-99-2P** 287953-01-9P
RL: PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(ultrasound imaging and treatment with targeted compns.)
IT 74-88-4, Iodomethane, reactions 108-00-9, N,N-Dimethylethylenediamine
143-27-1, Hexadecylamine 693-13-0, Diisopropylcarbodiimide 1069-79-0
4196-35-4 5505-63-5, D-Mannosamine hydrochloride 6066-82-6,
N-Hydroxysuccinimide 7087-68-5, Diisopropylethylamine 23911-25-3,
Ethylenediaminetetraacetic acid dianhydride 24991-53-5,
Polyethyleneglycol diamine 25322-68-3D, aminated amidated end groups
25322-68-3D, aminocarboxy and triethylamine salt derivs. 36653-82-4,
Hexadecyl alcohol 39927-08-7 55750-62-4 68181-17-9 108032-13-9
153345-74-5 287952-80-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(ultrasound imaging and treatment with targeted compns.)
IT 25322-68-3DP, Polyethylene glycol, aminocarboxy terminated 25322-68-3DP,
fluorinated stearoylphosphatidylethanolamine end groups 25322-68-3DP,
stearoylphosphatidylethanolamine, tert-butoxycarbonyl, aminated and
amidated end groups 56309-86-5P 186750-12-9P 186750-13-0P
186750-15-2P 186750-18-5P 186750-19-6P 186750-20-9P 186750-22-1P
186750-23-2P 186750-25-4P 186750-27-6P 186750-32-3P 221553-04-4P
221553-26-0P 287952-86-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(ultrasound imaging and treatment with targeted compns.)
IT 5681-36-7, Dipalmitoylphosphatidylethanolamine
RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(ultrasound imaging and treatment with targeted compns.)
IT 25322-68-3DP, fluorinated stearoylphosphatidylethanolamine and peptide end
groups 25322-68-3DP, stearoylphosphatidylethanolamine, aminated and
amidated end groups 186750-11-8P 186750-14-1P 186750-17-4P
186750-20-9DP, conjugates with protein A 186750-21-0P 186750-23-2DP,

conjugates with protein A 186750-24-3P 186750-26-5P 186750-28-7DP, conjugates with maleimido-labeled protein A 186750-28-7P 186750-29-8DP, conjugates with protein A 186750-29-8P 186750-31-2P 221553-48-6P 287952-90-3P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(ultrasound imaging and treatment with targeted compns.)

IT 50-70-4, Sorbitol, biological studies 56-81-5, 1,2,3-Propanetriol, biological studies 57-88-5, Cholesterol, biological studies 63-89-8, Dipalmitoylphosphatidylcholine 75-73-0, Perfluoromethane 76-16-4, Perfluoroethane 76-19-7, Perfluoropropane 99-20-7, Trehalose 115-25-3, Perfluorocyclobutane 355-25-9, Perfluorobutane 355-42-0, Perfluorohexane 678-26-2, Perfluoropentane 816-94-4, Distearoylphosphatidylcholine 2126-93-4D, Cholesteryl amine, reaction products with PEGylated dipalmitoylphosphatidylethanolamine 2462-63-7, Dioleoylphosphatidylethanolamine 4235-95-4 4537-78-4, Distearoylphosphatidylglycerol 7758-16-9, Disodium dihydrogen pyrophosphate 7778-77-0, Potassium dihydrogen phosphate 9002-89-5, Polyvinyl alcohol 9002-98-6, Polyethylenimine 9003-01-4, Poly(acrylic acid) 9003-39-8, Polyvinylpyrrolidone 9003-54-7, Acrylonitrile-styrene copolymer 9005-49-6, Heparin, biological studies 9011-14-7, Poly(methyl methacrylate) 9012-76-4D, Chitosan, reaction products with basic fibroblast growth factor 9016-00-6, Polydimethylsiloxane, SRU 9039-53-6, Urokinase 10043-52-4, Calcium chloride, biological studies 12629-01-5, Human growth hormone 18194-24-6, Dimyristoylphosphatidylcholine 18883-66-4, Streptozocin 19698-29-4, Dipalmitoyl phosphatidic acid 24980-41-4, Poly(ε-caprolactone) 24991-23-9 25087-26-7, Poly(methacrylic acid) 25248-42-4, Poly[oxy(1-oxo-1,6-hexanediyl)] 25322-68-3 25322-69-4, Polypropylene oxide 25513-46-6, Poly(glutamic acid) 25852-91-9 25852-91-9D, phenylcarboxy ester derivs. 26023-30-3, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)] 26100-51-6, Poly(lactic acid) 26913-06-4, Polyethylenimine 31900-57-9, Polydimethylsiloxane 78543-25-6, 1-Hexadecyl-2-palmitoylglycerophosphoethanolamine 80294-15-1 80755-87-9 97782-02-0 99896-85-2 100072-54-6D, conjugates with antibodies 106096-93-9, Basic fibroblast growth factor 106096-93-9D, Basic fibroblast growth factor, reaction products with chitosan 106392-12-5, Pluronic F-68 127464-60-2, Vascular endothelial growth factor 127464-60-2D, Vascular endothelial growth factor, reaction products with PEGylated distearoylphosphatidylethanolamine 145035-96-7D, DSPE-PEG, reaction products with vascular endothelial growth factor 145035-97-8, DPPE-PEG 145035-97-8D, DPPE-Peg, peptide conjugate 186750-22-1D, reaction products with cholesterylamine 208345-02-2, Acrylonitrile-vinylidene copolymer 208345-03-3, Acrylonitrile-methyl methacrylate vinylidene copolymer 221553-37-3 221553-49-7 287952-65-2
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ultrasound imaging and treatment with targeted compns.)

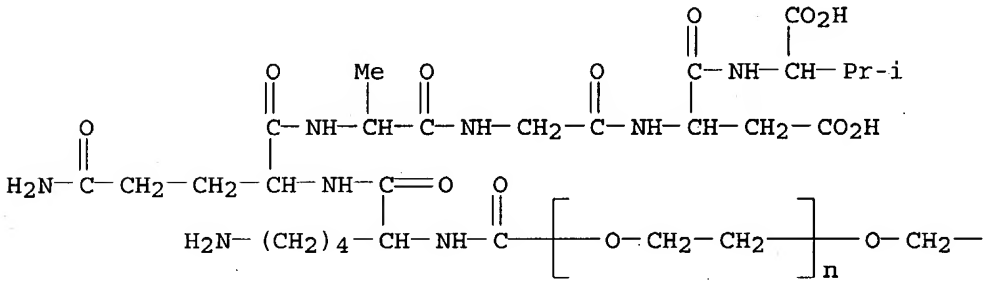
IT 158455-48-2 158455-49-3 288149-13-3 288149-14-4 288149-59-7 288149-60-0
RL: PRP (Properties)
(unclaimed protein sequence; novel methods of imaging and treatment with targeted compns.)

IT 127829-88-3, Trigramin γ (Trimeresurus gramineus reduced) 158053-05-5 288067-15-2 288067-16-3 288067-17-4 288067-18-5 288067-19-6 288067-20-9 288067-21-0
RL: PRP (Properties)
(unclaimed sequence; novel methods of imaging and treatment with targeted compns.)

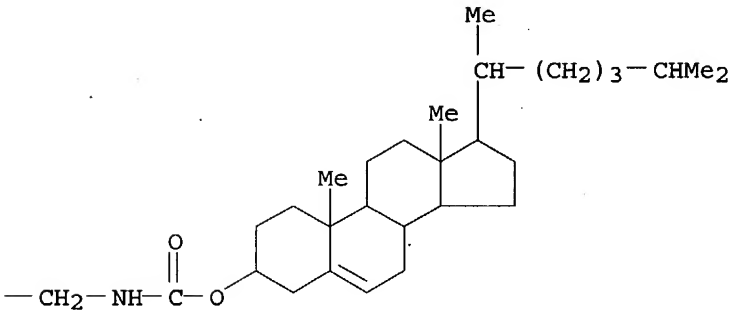
IT **287952-99-2P**
RL: PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(ultrasound imaging and treatment with targeted compns.)

RN 287952-99-2 HCAPLUS
CN Poly(oxy-1,2-ethanediyl), α-hydro-ω-[2-[[[(3β)-cholest-5-en-3-yloxy]carbonyl]amino]ethoxy]-, 1-ester with N2-carboxy-L-lysyl-L-glutaminyl-L-alanylglycyl-L-α-aspartyl-L-valine (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B



L106 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1981:565151 HCAPLUS
DN 95:165151
ED Entered STN: 12 May 1984
TI **Oligopeptides**, antisera containing them and methods of their use
IN Goldstein, Avram
PA Addiction Research Foundation, USA
SO Eur. Pat. Appl., 41 pp.
CODEN: EPXXDW
DT Patent
LA English
IC C07C103-52; A61K037-02
CC 9-13 (Biochemical Methods)
Section cross-reference(s): 2
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 29300	A1	19810527	EP 1980-303698	19801020
	EP 29300	B1	19840118		
	R: CH, DE, FR, GB, IT, NL, SE				
	US 4396606	A	19830802	US 1979-91615	19791105

	CA 1177825	A1	19841113	CA 1980-363326	19801027
	JP 56081550	A2	19810703	JP 1980-153943	19801104
	JP 02024838	B4	19900530		
PRAI	US 1979-91615		19791105		

AB **Oligopeptides** are described which have alternating basic **hydrophilic** and hydrophobic amino acids (≥5 units) and which are used as precursors for **conjugating** to **polypeptide opioids** (e.g., Leu-**enkephalin** and **Met-enkephalin**). The title compds. can be used as drugs. In 1 examples, a **tridecapeptide** was synthesized with the same amino acid sequence as porcine **dynorphin**-(1-13) (I). The potency of I was compared to compds. such as Leu-**enkephalin** by bioassay and radioreceptor binding assay. In addition, a radioimmunoassay was developed with antiserum against **dynorphin**-thyroglobulin **conjugate** and 125I-labeled I as tracer. Related peptides are also described, as well as their use in **opioid** receptor binding studies.

ST **oligopeptide** analgesic; radioimmunoassay analgesic **oligopeptide**; opiate receptor binding **oligopeptide**

IT Receptors
RL: SPN (Synthetic preparation); PREP (Preparation)
(for opiates, **oligopeptides** preparation for binding studies of)

IT Analgesia
(from opiates, anal. of, **oligopeptides** for radioimmunoassays in)

IT Thyroglobulins
RL: SPN (Synthetic preparation); PREP (Preparation)
(reaction products with **dynorphin**, preparation of, for radioimmunoassay)

IT Radiochemical analysis
(immunol., for **opioid oligopeptides**, analgesia in relation to)

IT **Peptides**, uses and miscellaneous
RL: SPN (Synthetic preparation); PREP (Preparation)
(**oligo**-, preparation and determination of, by radioimmunoassay, **opioid** analgesia in relation to)

IT Narcotics
RL: SPN (Synthetic preparation); PREP (Preparation)
(opium-like, **oligopeptides** as, preparation and determination of, by radioimmunoassay, analgesia in relation to)

IT Immunochemistry
(radioimmunoassay, for **opioid oligopeptides**, analgesia in relation to)

IT 72957-38-1P 79515-34-7P 79515-35-8P 79515-36-9P 79515-37-0P 79515-38-1P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and determination of, by radioimmunoassay, **opioid** analgesia in relation to)

IT 72957-38-1DP, reaction products with thyroglobulin
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, by radioimmunoassay, **opioid** analgesia in relation to)

IT 57-27-2DP, reaction products with **oligopeptides**
58569-55-4DP, reaction products with **oligopeptides**
58822-25-6DP, reaction products with **oligopeptides**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, for **opioid** receptor binding studies)

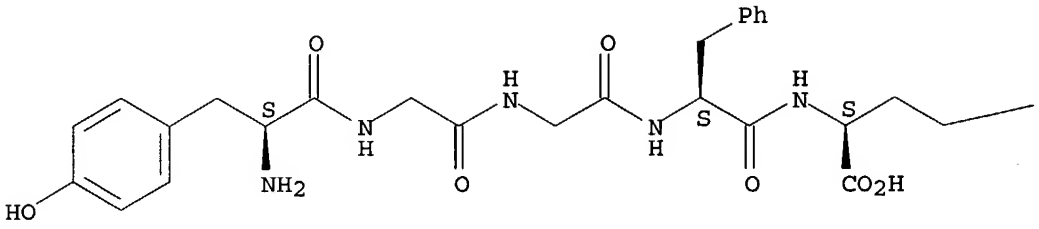
IT **58569-55-4DP**, reaction products with **oligopeptides**
58822-25-6DP, reaction products with **oligopeptides**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, for **opioid** receptor binding studies)

RN 58569-55-4 HCAPLUS

CN 1-5-Adrenorphin (human) (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

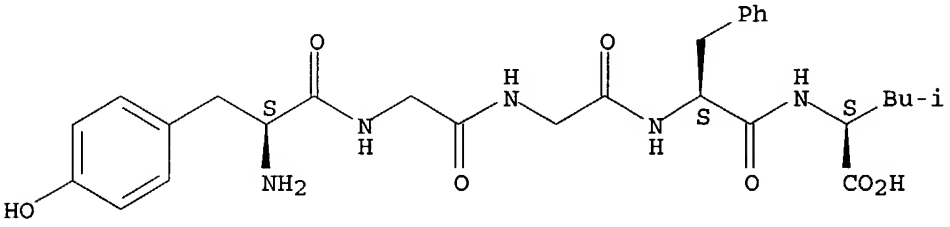


PAGE 1-B

— SMe

RN 58822-25-6 HCAPLUS
CN 1-5-β-Neoendorphin (human) (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L106 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1981:438681 HCAPLUS
DN 95:38681
ED Entered STN: 12 May 1984
TI Diaminotriacetic acid and its chelates bound on a substrate
IN Wieder, Irwin; Wollenberg, Robert H.
PA Analytical Radiation Corp., USA
SO Ger. Offen., 42 pp.
CODEN: GWXXBX
DT Patent
LA German
IC C07C103-50; C07J041-00; C07G007-00; C07G017-00
CC 9-6 (Biochemical Methods)
Section cross-reference(s): 2, 15
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 3033691	A1	19810319	DE 1980-3033691	19800908
	US 4352751	A	19821005	US 1979-73728	19790910
	GB 2060623	A	19810507	GB 1980-28730	19800905
	GB 2060623	B2	19840125		
	FR 2469416	A1	19810522	FR 1980-19459	19800909
	FR 2469416	B1	19840203		
	JP 56059741	A2	19810523	JP 1980-125857	19800910
	US 4432907	A	19840221	US 1981-260574	19810505

	US 4965211	A	19901023	US 1983-550504	19831109
	JP 60243052	A2	19851203	JP 1985-40240	19850228
	JP 60252684	A2	19851213	JP 1985-40241	19850228
PRAI	US 1979-73728		19790910		
	US 1981-260575		19810505		

OS CASREACT 95:38681

AB Diaminotriacetic acid-organic compound-metal-activator complexes are described for fluorescence assays, especially fluorescence immunoassays. In 1 example, thyroxine was bound to EDTA dianhydride, and the remaining anhydride group was hydrolyzed. The conjugate product, thyroxine-ethylenediaminetriacetic acid, was purified on a silica gel column and by TLC. A complex of Tb and the conjugate was formed. When a ternary complex was formed with 5-sulfosalicylate (as activator), it was used as a label in a fluorescence immunoassay for thyroxine. Examples are also given for preparation of other complexes and for detns. of antibodies, cells, thyronine and bacteria.

ST ethylenediaminetriacetate chelate fluorescence assay; thyroxine fluorescence immunoassay; antibody fluorescence immunoassay; cell fluorescence assay; bacteria fluorescence assay; thyronine fluorescence immunoassay; immunoassay fluorescence conjugate; alkylene diamine triacetate fluorescence assay; staining immunofluorescence conjugate

IT Antibodies
RL: ANT (Analyte); ANST (Analytical study)
(determination of, by fluorescence immunoassay, label preparation for)

IT Blood analysis
(thyroxine and IgE antibodies determination in, by fluorescence immunoassay, label preparation for)

IT Immunoglobulins
RL: ANT (Analyte); ANST (Analytical study)
(E, determination of, by fluorescence immunoassay, label preparation for)

IT Immunochemistry
(fluorescence immunoassay, alkylenediaminetriacetate chelates as labels in)

IT Spectrochemical analysis
(fluorometric, alkyldiaminetriacetate chelates as labels for)

IT Staining, biological
(immunofluorescent, alkylene diaminetriacetate chelates for)

IT 7440-00-8D, complexes with alkylenediaminetriacetate-organic compds. conjugates 7440-19-9D, complexes with alkylenediaminetriacetate-organic compds. conjugates
RL: ANST (Analytical study)
(as fluorescent labels in assays)

IT 51-48-9, analysis
RL: ANT (Analyte); ANST (Analytical study)
(determination of, by fluorescence immunoassay, label preparation for)

IT 51-48-9, analysis
RL: ANT (Analyte); ANST (Analytical study)
(determination of, in blood plasma by fluorescence immunoassay, label preparation for)

IT 77996-63-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and complexation of, with potassium carbonate)

IT 75-04-7P, uses and miscellaneous 77975-59-8P **77975-61-2P** 77975-63-4P 77975-68-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and hydrolysis of)

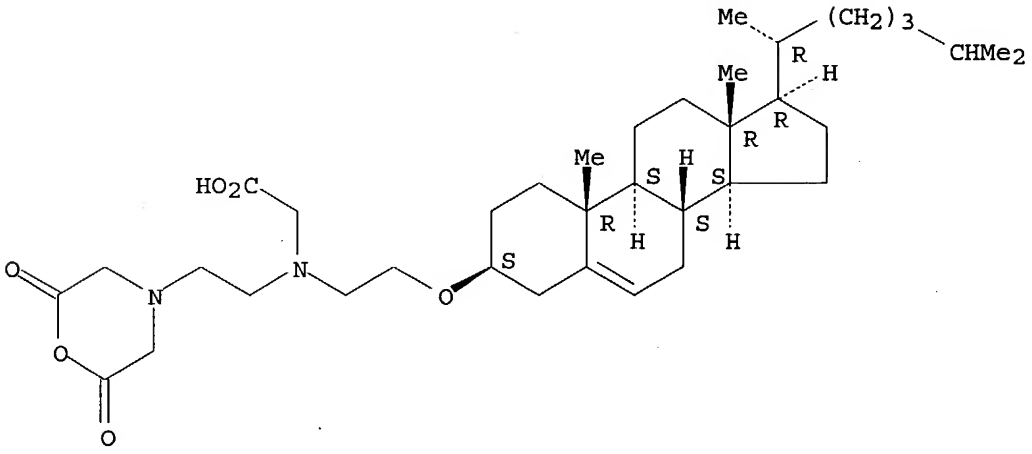
IT 77979-66-9P 77996-64-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with aminosalicylate)

IT 77975-69-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT

(Reactant or reagent)
(preparation and reaction of, with cobalt chloride or terbium bromide)
IT 77975-70-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with europium)
IT 77975-60-1P 77975-65-6P 77975-66-7P 77975-67-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with metals)
IT 23911-25-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with organic compds.)
IT 77979-69-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with sulfosalicylate or phenanthroline)
IT 77979-67-0P 77979-68-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with terbium chloride)
IT **77975-62-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with terbium or dysprosium)
IT 77975-64-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
IT 78216-66-7P 78216-67-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, for thyronine fluorescence immunoassay)
IT 78216-68-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, for thyroxine fluorescence immunoassay)
IT 108-24-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with EDTA)
IT 55-03-8 57-88-5, reactions 67-63-0, reactions 75-08-1 108-95-2, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with EDTA dianhydride)
IT 109-89-7, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with EDTA dianhydride or cyclohexanediaminetetraacetic anhydride)
IT 60-00-4, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with acetic anhydride)
IT 7440-53-1, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with cyclohexylenediaminetriacetate)
IT 584-08-7 78192-34-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with cyclohexylenediaminetriacetate-europium complex)
IT 63671-77-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with diethylamine)
IT 7429-91-6, reactions 7440-27-9, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with ethanolcholesterolethylenediaminetriacetic acid)
IT 97-05-2
RL: RCT (Reactant); RACT (Reactant or reagent)

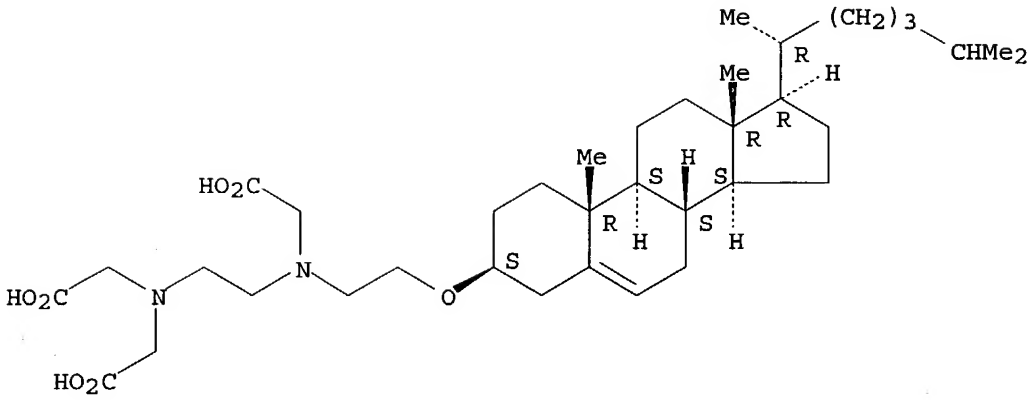
(reaction of, with ethylenediaminetriacetate-metal complexes)
IT 1596-67-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with propylenediaminetriacetate dianhydride)
IT 23910-53-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with thyronine)
IT 10241-04-0 14456-47-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with thyronine-propylenediaminetriacetate conjugate)
IT 65-49-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with thyronine-propylenediaminetriacetate-metal complexes)
IT 10025-76-0 10042-88-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with thyroxine-ethylenediaminetriacetate conjugate)
IT 66-71-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with thyroxine-ethylenediaminetriacetate-europium complex)
IT **77975-61-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and hydrolysis of)
RN 77975-61-2 HCAPLUS
CN Glycine, N-[[[(3β)-cholest-5-en-3-yl]oxy]ethyl]-N-[2-(2,6-dioxo-4-morpholinyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **77975-62-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with terbium or dysprosium)
RN 77975-62-3 HCAPLUS
CN Glycine, N-[2-[bis(carboxymethyl)amino]ethyl]-N-[2-[[(3β)-cholest-5-en-3-yl]oxy]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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L107 ANSWER 1 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2004:392055 HCAPLUS
DN 140:412314
ED Entered STN: 14 May 2004
TI **Calcitonin** drug-**oligomer conjugates**, and therapeutic uses for bone diseases
IN **Ekwuribe, Nnochiri N.**; **Radhakrishnan, Balasingam**
PA USA
SO U.S. Pat. Appl. Publ., 29 pp.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K038-17
ICS C07K014-56
NCL 424078370; 530307000
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 2
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2004091452	A1	20040513	US 2002-166355	20021108
WO 2004043347	A2	20040527	WO 2003-US33618	20031024

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2002-166355 A2 20021108
AB **Calcitonin** drug-**oligomer conjugates** that include a **calcitonin** drug coupled to an **oligomer** including a single polyalkylene glycol moiety consisting of between 4 and 10 polyalkylene glycol subunits are disclosed. Pharmaceutical compns. including such **conjugates** and methods of treating bone disorders by administering such **conjugates** are also disclosed. **Calcitonin** drug-**oligomer conjugates** according to embodiments of the present invention may lower serum calcium levels by

20 percent or more. Moreover, such **conjugates** may provide decreased degradation by intestinal enzymes and/or provide increased bioavailability when compared to non-**conjugated** **calcitonin.**

ST salmon **calcitonin** drug **oligomer conjugate** bone disease therapy

IT Polyoxyalkylenes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**calcitonin** drug-**oligomer conjugate** comprising; **calcitonin** drug-**oligomer** **conjugates**, and therapeutic uses for bone diseases)

IT Polyoxyalkylenes, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(**calcitonin** drug-**oligomer conjugates**, and therapeutic uses for bone diseases)

IT Salmon
(**calcitonin** drug; **calcitonin** drug-**oligomer** **conjugates**, and therapeutic uses for bone diseases)

IT Amines, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(function, of salmon **calcitonin**; **calcitonin** drug-**oligomer conjugates**, and therapeutic uses for bone diseases)

IT Drug delivery systems
(oral; **calcitonin** drug-**oligomer conjugates** , and therapeutic uses for bone diseases)

IT Bone, disease
(treatment of; **calcitonin** drug-**oligomer** **conjugates**, and therapeutic uses for bone diseases)

IT 100-44-7, Benzyl chloride, reactions 109-86-4, Ethylene glycol mono methyl ether 112-35-6, Triethylene glycol monomethyl ether 112-60-7, Tetraethylene glycol 112-76-5, Stearoyl chloride 124-63-0, Methanesulfonyl chloride 865-47-4 6066-82-6, N-Hydroxysuccinimide 25322-68-3, PEG6 47931-85-1, **Calcitonin**(salmon)
RL: RCT (Reactant); RACT (Reactant or reagent)
(**calcitonin** drug-**oligomer conjugates**, and therapeutic uses for bone diseases)

IT 1679-53-4P, 10-Hydroxydecanoic acid 3639-35-8P 4437-01-8P, 2,5,8,11,14,17,20-Heptaoxadocosan-22-ol 5702-16-9P 6048-68-6P 25990-96-9P 27425-92-9P 29823-21-0P 70802-40-3P 73018-92-5P 74654-05-0P 86259-87-2P, Tetraethylene glycol monobenzylether 114740-40-8P 477775-57-8P 477775-65-8P 477775-66-9P 477775-67-0P 477775-68-1P 477775-69-2P 477775-70-5P 477775-73-8P 477775-74-9P 477775-76-1P 477781-68-3P 477781-69-4P 688753-51-7P 688753-52-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(**calcitonin** drug-**oligomer conjugates**, and therapeutic uses for bone diseases)

IT 47931-85-1DP, **Calcitonin**(salmon), **conjugates** with **oligomers** 477775-66-9DP, **conjugates** with **calcitonin**(salmon) 477775-70-5DP, **conjugates** with **calcitonin**(salmon) 477775-76-1DP, **conjugates** with **calcitonin**(salmon) 688753-52-8DP, **conjugates** with **calcitonin**(salmon)
RL: SPN (Synthetic preparation); PREP (Preparation)
(**calcitonin** drug-**oligomer conjugates**, and therapeutic uses for bone diseases)

L107 ANSWER 2 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2004:226560 HCAPLUS
ED Entered STN: 21 Mar 2004
TI Strategies toward the oral delivery of insulin: Using molecular modification to solve drug delivery challenges

AU Riggs-Sauthier, Jennifer A.; James, Kenneth D.; Malkar, Navdeep; Miller, Mark A.; Dugdell, Robert E.; Burgess, Krisstina S. Danek; Severynse-Stevens, Diana; Surguladze, David; **Ekwuribe, Nnochiri**
CS Drug Discovery & Chemical Innovation, **Nobex** Corporation, Research Triangle Park, NC, 27709, USA
SO Abstracts of Papers, 227th ACS National Meeting, Anaheim, CA, United States, March 28-April 1, 2004 (2004), MEDI-202 Publisher: American Chemical Society, Washington, D. C.
CODEN: 69FGKM
DT Conference; Meeting Abstract
LA English
AB While the **conjugation** of polyethylene glycol (PEG) to **protein** and **peptide** therapeutics is well known to enhance the aqueous solubility, render proteins non-immunogenic, reduce kidney clearance rate, and increase the circulation time of the parent **peptide**, the high mol. wts. that are commonly used preclude oral delivery of the therapeutic. Nobex Corporation has proprietary **amphiphilic oligomers** of PEG and alkyl combinations that have been successfully applied to several **peptide** therapeutics to enhance their PK/PD profiles and enable oral delivery. In an effort to understand the effects of **conjugating** these **amphiphilic oligomers** to insulin and develop structure relationship activities, a broad range of insulin **conjugates** varying in size, sterics, and **amphiphilic** balance were synthesized. The **conjugates** were screened by in vitro and in vivo assays to measure activity and determine oral bioefficacy. In addition, many physicochem. properties such as aqueous solubility, protease stability, CD (CD), and thermal denaturation (Tm) were evaluated.

L107 ANSWER 3 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:1006707 HCAPLUS
DN 140:35957
ED Entered STN: 26 Dec 2003
TI Methods of reducing hypoglycemic episodes in the treatment of diabetes mellitus by orally administering an insulin-**oligomer conjugate**
IN Still, James Gordon; Kosutic, Gordana
PA **Nobex Corporation, USA**
SO PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K
CC 1-10 (Pharmacology)
Section cross-reference(s): 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003105768	A2	20031224	WO 2003-US18763	20030613
	WO 2003105768	A3	20040311		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2004038867	A1	20040226	US 2003-461199	20030613
PRAI	US 2002-388988P	P	20020613		

OS MARPAT 140:35957

AB The present invention provides compns. and methods for reducing hypoglycemic episodes experienced by a subject in need of treatment for diabetes mellitus, said method comprising orally administering an amount of an insulin **polypeptide-oligomer conjugate** to the subject, wherein: (i) the amount of the insulin **polypeptide-oligomer conjugate** reduces the number and/or severity of hypoglycemic episodes experienced by the subject during a given time period when compared with the number and/or severity of hypoglycemic episodes that would have been experienced during a similar time period by the subject or by subjects in a control group parenterally administered insulin or an insulin analog in an amount that provides a substantially equivalent level of glycemic control; and (ii) the **oligomer** of the insulin **polypeptide-oligomer conjugate** comprises a **hydrophilic** moiety and a **lipophilic** moiety. Patients with type 1 diabetes were treated p.o. with HIM2 (human insulin with -C(O)(CH2)5(OC2H4)7OCH3 **conjugated** to the B29 lysine) in comparison with treatment with insulin lispro, s.c. Hypoglycemic events that required rescue intervention were significantly lower in the HIM2 treatment group as compared to the insulin lispro treatment group.

ST insulin **conjugate** reducing hypoglycemic episode diabetes mellitus; oral insulin **oligomer conjugate** hypoglycemia redn antidiabetic; HIM2 oral antidiabetic redn hypoglycemic episode

IT Drug delivery systems
(capsules; oral insulin-**oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)

IT **Oligomers**
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**hydrophilic-lipophilic**, **conjugates** with insulin; oral insulin-**oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)

IT Diabetes mellitus
(insulin-dependent; oral insulin-**oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)

IT Drug delivery systems
(liqs., oral; oral insulin-**oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)

IT **Hydrophilicity**
Lipophilicity
(of **oligomer**; oral insulin-**oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)

IT Diabetes mellitus
Human
Hypoglycemia
Postprandial period
(oral insulin-**oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)

IT Antidiabetic agents
(oral; oral insulin-**oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)

IT Flavoring materials
(strawberry; oral insulin-**oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)

IT 50-99-7, D-Glucose, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(HIM2 **conjugate** maintenance of two-hour postprandial blood levels of; oral insulin-**oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)

IT 9035-68-1, Proinsulin
RL: RCT (Reactant); RACT (Reactant or reagent)

(acylation **conjugation** of; oral insulin-**oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)

IT **9002-07-7, Trypsin** 9025-24-5, Carboxypeptidase B
RL: CAT (Catalyst use); USES (Uses)
(in HIM2 **conjugate** preparation from proinsulin; oral insulin-**oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)

IT 223714-27-0P
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(oral insulin-**oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)

IT 9004-10-8D, Insulin, **conjugates** with **hydrophilic-lipophilic oligomer** 502487-21-0D, **conjugates** with insulin
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral insulin-**oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)

IT 57-55-6, Propylene glycol, biological studies 77-86-1, Tris(hydroxymethyl)aminomethane 77-92-9, Citric acid, biological studies 102-71-6, Triethanolamine, biological studies 112-80-1, Oleic acid, biological studies 143-07-7, Lauric acid, biological studies 334-48-5, Capric acid 361-09-1, Sodium cholate 1310-73-2, Sodium hydroxide, biological studies 7632-05-5, Sodium phosphate 7732-18-5, Water, biological studies 56038-13-2, Sucralose
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral insulin-**oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)

L107 ANSWER 4 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:971710 HCAPLUS
DN 140:16981
ED Entered STN: 14 Dec 2003
TI Methods of synthesizing insulin **polypeptide-oligomer conjugates** and proinsulin **polypeptide-oligomer conjugates**
IN Soltero, Richard; **Radhakrishnan, Balasingam; Ekwuribe, Nnochiri N.**
PA USA
SO U.S. Pat. Appl. Publ., 101 pp., Cont.-in-part of U.S. Pat. Appl. 2003 87,808.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K038-28
ICS C07K014-62
NCL 514003000; 530303000
CC 34-3 (**Amino Acids, Peptides**, and **Proteins**)
Section cross-reference(s): 2
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003229009	A1	20031211	US 2003-382022	20030305
	US 2003087808	A1	20030508	US 2001-36744	20011221
	US 2003228652	A1	20031211	US 2003-389499	20030317
PRAI	US 2001-318197P	P	20010907		
	US 2001-36744	A2	20011221		
	US 2003-382022	A2	20030305		

OS MARPAT 140:16981

AB The invention provides a method for synthesizing an insulin **polypeptide-oligomer conjugate** that includes contacting a proinsulin **polypeptide**, comprising an insulin **polypeptide** coupled to one or more peptides by **peptide** bond(s) capable of being cleaved to yield the insulin **polypeptide**, with an **oligomer** under conditions sufficient to couple the **oligomer** to the insulin **polypeptide** portion of the proinsulin **polypeptide** and provide a proinsulin **polypeptide-oligomer conjugate**, and cleaving the one or more peptides from the proinsulin **polypeptide-oligomer conjugate** to provide the insulin **polypeptide-oligomer conjugate.**

ST proinsulin insulin **conjugate** C **peptide** drug delivery

IT Antidiabetic agents
Drug delivery systems
(synthesis of insulin **polypeptide-oligomer conjugates** and proinsulin **polypeptide-oligomer conjugates**)

IT 9004-10-8DP, Insulin, **conjugates** 9035-68-1DP, Proinsulin, **conjugates**
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis of insulin **polypeptide-oligomer conjugates** and proinsulin **polypeptide-oligomer conjugates**)

IT 56-87-1, Lysine, biological studies
RL: BSU (Biological study, unclassified); REM (Removal or disposal); BIOL (Biological study); PROC (Process)
(synthesis of insulin **polypeptide-oligomer conjugates** and proinsulin **polypeptide-oligomer conjugates**)

IT **9002-07-7, Trypsin** 9025-24-5, Carboxy peptidase b
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(synthesis of insulin **polypeptide-oligomer conjugates** and proinsulin **polypeptide-oligomer conjugates**)

IT 111-77-3, Diethylene glycol monomethyl ether 112-35-6, Triethylene glycol monomethyl ether 112-60-7, Tetraethylene glycol 623-65-4, Palmitic anhydride 865-47-4 5299-60-5, Ethyl 6-hydroxyhexanoate 17696-11-6, 8-Bromooctanoic acid 24342-68-5, Hexaethylene glycol monobenzyl ether 74124-79-1, N,N'-Disuccinimidyl carbonate
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of insulin **polypeptide-oligomer conjugates** and proinsulin **polypeptide-oligomer conjugates**)

IT 4437-01-8P, Heptaethylene glycol monomethyl ether 27425-92-9P, Decaethylene glycol monomethyl ether 74654-05-0P 124668-93-5P 130955-39-4P 477775-57-8P 477775-58-9P 477775-59-0P 477775-60-3P 477775-65-8P 477775-66-9P 477775-70-5P 477775-76-1P 477775-77-2P 477781-68-3P 502487-20-9P 502487-21-0P 502487-22-1P 502487-24-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of insulin **polypeptide-oligomer conjugates** and proinsulin **polypeptide-oligomer conjugates**)

IT 59112-80-0D, c **Peptide, conjugates**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesis of insulin **polypeptide-oligomer conjugates** and proinsulin **polypeptide-oligomer conjugates**)

L107 ANSWER 5 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:971618 HCAPLUS
DN 140:16980
ED Entered STN: 14 Dec 2003
TI Methods of synthesizing insulin **polypeptide-oligomer conjugates** and proinsulin **polypeptide-oligomer conjugates**
IN **Radhakrishnan, Balasingam**; Soltero, Richard; **Ekwuribe, Nnochiri N.**; Puskas, Monica; Sangal, Diti
PA USA
SO U.S. Pat. Appl. Publ., 102 pp., Cont.-in-part of U.S. Ser. No. 382,022.
CODEN: USXXCO
DT Patent
LA English
IC ICM C12P021-06
ICS A61K038-28
NCL 435068100; 530303000
CC 34-3 (**Amino Acids**, **Peptides**, and **Proteins**)
Section cross-reference(s): 2
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003228652	A1	20031211	US 2003-389499	20030317
	US 2003087808	A1	20030508	US 2001-36744	20011221
	US 2003229009	A1	20031211	US 2003-382022	20030305
PRAI	US 2001-318197P	P	20010907		
	US 2001-36744	A2	20011221		
	US 2003-382022	A2	20030305		

OS MARPAT 140:16980
AB The invention provides a method for synthesizing an insulin **polypeptide-oligomer conjugate** that includes contacting a proinsulin **polypeptide**, comprising an insulin **polypeptide** coupled to one or more peptides by **peptide** bond(s) capable of being cleaved to yield the insulin **polypeptide**, with an **oligomer** under conditions sufficient to couple the **oligomer** to the insulin **polypeptide** portion of the proinsulin **polypeptide** and provide a proinsulin **polypeptide-oligomer conjugate**, and cleaving the one or more peptides from the proinsulin **polypeptide-oligomer conjugate** to provide the insulin **polypeptide-oligomer conjugate.**
ST proinsulin insulin **conjugate** C **peptide** drug delivery
IT Antidiabetic agents
Drug delivery systems
(synthesis of insulin **polypeptide-oligomer conjugates** and proinsulin **polypeptide-oligomer conjugates**)
IT 9004-10-8DP, Insulin, **conjugates** 9035-68-1DP, Proinsulin, **conjugates**
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis of insulin **polypeptide-oligomer conjugates** and proinsulin **polypeptide-oligomer conjugates**)
IT 56-87-1, Lysine, biological studies
RL: BSU (Biological study, unclassified); REM (Removal or disposal); BIOL (Biological study); PROC (Process)
(synthesis of insulin **polypeptide-oligomer conjugates** and proinsulin **polypeptide-oligomer conjugates**)
IT **9002-07-7**, **Trypsin** 9025-24-5, Carboxy peptidase b

RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(synthesis of insulin **polypeptide-oligomer conjugates** and proinsulin **polypeptide-oligomer conjugates**)

IT 111-77-3, Diethylene glycol monomethyl ether 112-35-6, Triethylene glycol monomethyl ether 112-60-7, Tetraethylene glycol 623-65-4, Palmitic anhydride 865-47-4 5299-60-5, Ethyl 6-hydroxyhexanoate 17696-11-6, 8-Bromooctanoic acid 24342-68-5, Hexaethylene glycol monobenzyl ether 74124-79-1, N,N'-Disuccinimidyl carbonate
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of insulin **polypeptide-oligomer conjugates** and proinsulin **polypeptide-oligomer conjugates**)

IT 4437-01-8P, Heptaethylene glycol monomethyl ether 27425-92-9P, Decaethylene glycol monomethyl ether 74654-05-0P 124668-93-5P 130955-39-4P 477775-57-8P 477775-58-9P 477775-59-0P 477775-60-3P 477775-65-8P 477775-66-9P 477775-70-5P 477775-76-1P 477775-77-2P 477781-68-3P 502487-20-9P 502487-21-0P 502487-22-1P 502487-24-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of insulin **polypeptide-oligomer conjugates** and proinsulin **polypeptide-oligomer conjugates**)

IT 59112-80-0D, c **Peptide, conjugates**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesis of insulin **polypeptide-oligomer conjugates** and proinsulin **polypeptide-oligomer conjugates**)

L107 ANSWER 6 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:633486 HCAPLUS
DN 139:185669
ED Entered STN: 15 Aug 2003
TI Polymers for delivering peptides and small molecules in vivo
IN **Ansari, Aslam M.**; Scaria, Puthupparampil V.; Woodle, Martin C.
PA Intradigm Corporation, USA
SO PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-74
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 37
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003066069	A1	20030814	WO 2003-US2710	20030131

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2002-352881P P 20020201
AB Certain **hydrophilic** polymers, such as a polyoxazoline, when **conjugated** to a **polypeptide** or small mol. agent, can enhance the bioavailability of the agent when administered in vivo.

Accordingly, **hydrophilic** polymers of the invention can be used as a delivery vehicle to treat any number of disorders and/or confer a myriad of therapeutic benefits to a subject. Examples polymers include H2N-ACRGDMFCA-end capped polymethyl- or poly(ethyloxazoline).

ST polyoxazoline drug delivery; **peptide** delivery polymer

IT Polyoxyalkylenes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(derivs.; polymers for delivering peptides and small mols. in vivo)

IT Drug delivery systems
(polymers for delivering peptides and small mols. in vivo)

IT Nucleic acids
Peptides, biological studies
Polyamines
Polyesters, biological studies
Polyoxymethylenes, biological studies
Proteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polymers for delivering peptides and small mols. in vivo)

IT 25805-17-8DP, Poly(2-ethyloxazoline), reaction products with peptides
26375-28-0DP, Poly(2-methyloxazoline), reaction products with peptides
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(polymers for delivering peptides and small mols. in vivo)

IT 25322-68-3D, Peg, derivs. 26009-03-0D, Polyglycolic acid, derivs. 26023-30-3D, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)], derivs. 26100-51-6D, Polylactic acid, derivs. 26124-68-5D, Polyglycolic acid, derivs. 34728-17-1D, Oxazole, 4,5-dihydro-, homopolymer, derivs. 577973-26-3D, reaction products with polyoxazolines
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polymers for delivering peptides and small mols. in vivo)

RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Koyama; US 5130126 A 1992 HCAPLUS

L107 ANSWER 7 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2003:221806 HCAPLUS

DN 138:260413

ED Entered STN: 21 Mar 2003

TI Methods of synthesizing insulin **polypeptide-oligomer conjugates**, and proinsulin **polypeptide-oligomer conjugates** and methods of synthesizing same

IN Soltero, Richard; **Radhakrishnan, Balasingham**; **Ekwuribe, Nnochiri N.**

PA **Nobex Corporation, USA**

SO PCT Int. Appl., 113 pp.
CODEN: PIXXD2

DT Patent

LA English

IC ICM C12N

CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 2

FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003022996	A2	20030320	WO 2002-US28428	20020906
	WO 2003022996	A3	20031231		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003087808 A1 20030508 US 2001-36744 20011221
EP 1430082 A2 20040623 EP 2002-766246 20020906
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK

PRAI US 2001-318197P P 20010907
US 2001-36744 A 20011221
US 2002-349462P P 20020118
WO 2002-US28428 W 20020906

OS MARPAT 138:260413

AB Methods for synthesizing proinsulin polypeptides are described that include a contacting a proinsulin **polypeptide** including an insulin **polypeptide** coupled to one or more peptides by **peptide** bond(s) capable of being cleaved to yield the insulin **polypeptide** with an **oligomer** under conditions sufficient to couple the **oligomer** to the insulin **polypeptide** portion of the proinsulin **polypeptide** and provide a proinsulin **polypeptide-oligomer conjugate**, and cleaving the one or more peptides from the proinsulin **polypeptide-oligomer conjugate** to provide the insulin **polypeptide-oligomer conjugate.** Methods of synthesizing proinsulin **polypeptide-oligomer conjugates** are also described as are proinsulin **polypeptide-oligomer conjugates.** Methods of synthesizing C-**peptide polypeptide-oligomer conjugates** are also described.

ST proinsulin insulin **conjugate** C **peptide** drug delivery

IT Antidiabetic agents
Drug delivery systems
(synthesizing insulin **polypeptide-oligomer conjugates** and proinsulin **polypeptide-oligomer conjugates**)

IT 9004-10-8DP, Insulin, **conjugates** 9035-68-1DP, Proinsulin, **conjugates**
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesizing insulin **polypeptide-oligomer conjugates** and proinsulin **polypeptide-oligomer conjugates**)

IT 56-87-1, Lysine, biological studies
RL: BSU (Biological study, unclassified); REM (Removal or disposal); BIOL (Biological study); PROC (Process)
(synthesizing insulin **polypeptide-oligomer conjugates** and proinsulin **polypeptide-oligomer conjugates**)

IT **9002-07-7, Trypsin** 9025-24-5, Carboxy peptidase b
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(synthesizing insulin **polypeptide-oligomer conjugates** and proinsulin **polypeptide-oligomer conjugates**)

IT 111-77-3, Diethylene glycol monomethyl ether 112-35-6, Triethylene glycol monomethyl ether 112-60-7, Tetraethylene glycol 623-65-4, Palmitic anhydride 865-47-4 5299-60-5, Ethyl 6-hydroxyhexanoate 17696-11-6, 8-Bromooctanoic acid 24342-68-5, Hexaethylene glycol monobenzyl ether 74124-79-1, N,N'-Disuccinimidyl carbonate
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesizing insulin **polypeptide-oligomer conjugates** and proinsulin **polypeptide-**

oligomer conjugates)
IT 4437-01-8P, Heptaethylene glycol monomethyl ether 27425-92-9P, Decaethylene glycol monomethyl ether 74654-05-0P 124668-93-5P 130955-39-4P 477775-57-8P 477775-58-9P 477775-59-0P 477775-60-3P 477775-65-8P 477775-66-9P 477775-70-5P 477775-76-1P 477775-77-2P 477781-68-3P 502487-20-9P 502487-21-0P 502487-22-1P 502487-24-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesizing insulin **polypeptide-oligomer conjugates** and proinsulin **polypeptide-oligomer conjugates**)
IT 59112-80-0D, c **Peptide, conjugates**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesizing insulin **polypeptide-oligomer conjugates** and proinsulin **polypeptide-oligomer conjugates**)

L107 ANSWER 8 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:221462 HCAPLUS
DN 138:260437
ED Entered STN: 21 Mar 2003
TI Pharmaceutical compositions of drug-**oligomer conjugates** for oral administration
IN Soltero, Richard; **Ekwuribe, Nnochiri N.**; Opawale, Foyeke; Rehlaender, Bruce; Hickey, Anthony; Bovet, Li Li
PA **Nobex Corporation, USA**
SO PCT Int. Appl., 96 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 2, 35
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003022210	A2	20030320	WO 2002-US28536	20020906
	WO 2003022210	A3	20031218		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2003083232	A1	20030501	US 2002-235381	20020905
PRAI	US 2001-318193P	P	20010907		
	US 2002-377865P	P	20020503		

AB An oral pharmaceutical composition comprising a drug-**oligomer conjugate**, 0.1-15% of a fatty acid component, and 0.1-15% of a bile salt component is described. The drug, e.g., a **peptide** or **protein**, is covalently coupled to an **oligomeric** moiety. The fatty acid component and the bile salt component are present in a weight-to-weight ratio of between 1:5 and 5:1. Methods of treating diseases in a subject in need of such treatment using such pharmaceutical compns. are also provided, as are methods of providing such pharmaceutical compns. For example, tablets containing an insulin **conjugate** HIM2 were prepared by lyophilization of a mixture containing HIM2 2.5 g, Na cholate 30.0 g,

oleic acid 10.0 g, 25% sucralose 8.0 g, flavor 4.0 g, capric acid 5.0 g, lauric acid 5.0 g, citric acid 67.2 g, trolamine 42.4 g, NaOH 18.8 g, pH adjusters (5N NaOH and 5N HCl) as needed, and water resulting in an amorphous powder. The powder (127.6 g) was blended with citric acid 29.7 g, sodium citrate 84.2 g, Tris base 106.7 g, microcryst. cellulose 24.8 g, and Explotab 9.4 g and compressed into tablets.

ST oral drug **oligomer conjugate** bile salt fatty acid; **peptide protein** drug **oligomer conjugate** oral

IT Drug delivery systems
(liqs., oral; oral compns. of drug-**oligomer conjugates** containing bile salt and fatty acid)

IT Fatty acids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(long-chain; oral compns. of drug-**oligomer conjugates** containing bile salt and fatty acid)

IT Fatty acids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(medium-chain; oral compns. of drug-**oligomer conjugates** containing bile salt and fatty acid)

IT Antidiabetic agents
Buffers
Human
(oral compns. of drug-**oligomer conjugates** containing bile salt and fatty acid)

IT Bile salts
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral compns. of drug-**oligomer conjugates** containing bile salt and fatty acid)

IT Drug delivery systems
(oral; oral compns. of drug-**oligomer conjugates** containing bile salt and fatty acid)

IT Drug delivery systems
(tablets; oral compns. of drug-**oligomer conjugates** containing bile salt and fatty acid)

IT 11061-68-0D, Human insulin, **conjugates** with methoxy(polyethylene glycol) hexanoic acid 326892-09-5D, **conjugates** with human insulin
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral compns. of drug-**oligomer conjugates** containing bile salt and fatty acid)

IT **9007-12-9D, Calcitonin, oligomer conjugates** 59112-80-0D, C-**Peptide, oligomer conjugates**
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral compns. of drug-**oligomer conjugates** containing bile salt and fatty acid)

IT 77-86-1, Tromethamine 102-71-6, Trolamine, biological studies 112-80-1, Oleic acid, biological studies 143-07-7, Lauric acid, biological studies 334-48-5, Capric acid 361-09-1, Sodium cholate 47931-85-1D, Salmon **calcitonin, oligomer conjugates** 477775-65-8D, drug **conjugates**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral compns. of drug-**oligomer conjugates** containing bile salt and fatty acid)

IT 100-44-7, Benzyl chloride, reactions 111-77-3, Diethylene glycol monomethyl ether 112-35-6, Triethylene glycol monomethyl ether 112-60-7, Tetraethylene glycol 112-76-5, Stearoyl chloride 1679-53-4, 10-Hydroxydecanoic acid 2615-15-8, Hexaethylene glycol 5299-60-5, Ethyl 6-hydroxyhexanoate 6066-82-6, N-Hydroxysuccinimide 17696-11-6, 8-Bromooctanoic acid

RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of **oligomers** for drug-**oligomer conjugates** for oral delivery)

IT 3639-35-8P 4437-01-8P, 2,5,8,11,14,17,20-Heptaoxadocosan-22-ol
10108-28-8P 24342-68-5P 27425-92-9P 29823-21-0P 60037-74-3P
74654-05-0P 86259-87-2P 113395-48-5P 124668-93-5P 477775-57-8P
477775-58-9P 477775-59-0P 477775-60-3P 477775-65-8P 477775-66-9P
477775-68-1P 477775-69-2P 477775-70-5P 477775-73-8P 477775-74-9P
477775-75-0P 477775-76-1P 477775-77-2P 477781-68-3P 477781-69-4P
477788-13-9P 502487-20-9P 502487-21-0P 502487-22-1P 502487-23-2P
502487-24-3P 502487-25-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of **oligomers** for drug-**oligomer conjugates** for oral delivery)

L107 ANSWER 9 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:221460 HCAPLUS
DN 138:260435
ED Entered STN: 21 Mar 2003
TI Pharmaceutical compositions of insulin drug-**oligomer conjugates**
IN Soltero, Richard; **Radhakrishnan, Balasingham; Ekwuribe, Nnochiri N.**; Rehlaender, Bruce; Hickey, Anthony; Bovet, Li Li
PA **Nobex Corporation, USA**
SO PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, **34**, 35
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003022208	A2	20030320	WO 2002-US28429	20020906
	WO 2003022208	A3	20030925		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2003083232	A1	20030501	US 2002-235381	20020905
PRAI	US 2001-318193P	P	20010907		
	US 2002-377865P	P	20020503		

OS MARPAT 138:260435
AB Pharmaceutical compns. that include an insulin drug-**oligomer conjugate**, a fatty acid component, and a bile salt component are described. The insulin drug is covalently coupled to an **oligomeric** moiety. The fatty acid component and the bile salt component are present in a weight-to-weight ratio of between 1:5 and 5:1. Methods of treating an insulin deficiency in a subject in need of such treatment using such pharmaceutical compns. are also provided, as are methods of providing such pharmaceutical compns. E.g., PEG derivs. of fatty acids such as hexanoic acid were prepared, activated and **conjugated** to insulin derivs.
ST insulin PEG fatty acid **conjugate** pharmaceutical

IT Drug delivery systems
(oral; pharmaceutical compns. of insulin drug-**oligomer conjugates**)
IT Drug delivery systems
(solids; pharmaceutical compns. of insulin drug-**oligomer conjugates**)
IT 361-09-1, Sodium cholate
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. of insulin drug-**oligomer conjugates**)
IT 111-77-3 112-35-6 112-60-7 112-76-5, Stearoyl chloride 623-65-4, Palmitic anhydride 2615-15-8 15848-88-1 23601-40-3, 2,5,8,11,14,17-Hexaoxanonadecan-19-ol 142556-85-2 477788-13-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(pharmaceutical compns. of insulin drug-**oligomer conjugates**)
IT 3639-35-8P, Decanoic acid, 10-hydroxy-, ethyl ester 4437-01-8P, 2,5,8,11,14,17,20-Heptaoxadocosan-22-ol 5299-60-5P, Ethyl 6-hydroxyhexanoate 10108-28-8P 24342-68-5P, Hexaethylene glycol monobenzyl ether 27425-92-9P, Decaethylene glycol monomethyl ether 29823-21-0P, Ethyl 8-bromooctanoate 60037-74-3P 74654-05-0P 86259-87-2P 105292-71-5P 113395-48-5P 124668-93-5P 259228-98-3P 477775-57-8P 477775-58-9P 477775-59-0P 477775-60-3P 477775-65-8P 477775-66-9P 477775-68-1P 477775-69-2P 477775-70-5P 477775-73-8P 477775-74-9P 477775-75-0P 477775-76-1P 477775-77-2P 477781-68-3P 477781-69-4P 502487-20-9P 502487-21-0P 502487-22-1P 502487-23-2P 502487-24-3P 502487-25-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(pharmaceutical compns. of insulin drug-**oligomer conjugates**)
IT 9004-10-8DP, Insulin, **conjugates** with fatty acid-PEG derivs.
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(pharmaceutical compns. of insulin drug-**oligomer conjugates**)
IT 502495-05-8 502495-19-4 502495-22-9 502495-24-1 502495-25-2 502495-35-4 502495-36-5 502495-38-7 502495-39-8 502495-40-1 502495-41-2 502495-42-3 502495-43-4 502495-44-5 502495-47-8 502495-48-9 502495-51-4 502495-52-5 502495-53-6
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. of insulin drug-**oligomer conjugates**)

L107 ANSWER 10 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:184235 HCAPLUS
ED Entered STN: 11 Mar 2003
TI Effects of **amphiphilic oligomers** on oral insulin **conjugates.** Part 3: Solubility and protease stability
AU James, Kenneth D.; Willie, Kirsten; Malkar, Navdeep B.; Severynse-Stevens, Diana; **Ekwuribe, Nnochiri N.**
CS Innovation and Drug Discovery, **Nobex** Corporation, Durham, NC, 27713, USA
SO Abstracts of Papers, 225th ACS National Meeting, New Orleans, LA, United States, March 23-27, 2003 (2003), MEDI-269 Publisher: American Chemical Society, Washington, D. C.
CODEN: 69DSA4
DT Conference; Meeting Abstract
LA English
AB The **conjugation** of polymers (such as polyethylene glycol; PEG) to **peptide** therapeutics has been known to increase the aqueous solubility and the circulation time of the parent **peptide.** Although the

resultant **peptide conjugate** may have an improved pharmacodynamic profile, the large **oligomers** that are commonly used preclude oral delivery of the therapeutic. Nobex Corporation has proprietary **amphiphilic oligomers** (polyoxyethylene alkyl ethers) that have been applied to several **peptide** therapeutics to enhance their PK/PD profile and enable oral delivery. We now present a study of the SAR and physicochem. properties of a series of insulin **conjugates** in which the **oligomers** vary in size, sterics, and **amphiphilic** balance. In Part 3 of this study, we assess the effects of various **oligomers** on solubility at varying pH and salt concns. We also evaluate stability of the resultant **conjugates** to the digestive enzymes **trypsin**, **chymotrypsin**, and pepsin.

L107 ANSWER 11 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:184234 HCAPLUS
ED Entered STN: 11 Mar 2003
TI Effects of **amphiphilic oligomers** on oral insulin **conjugates**. Part 2: Conformational changes of **conjugates**
AU Malkar, Navdeep; Juska, Darius; Fields, Gregg B.; **Ekwuribe, Nnochiri N.**; James, Kenneth D.
CS **Nobex Corporation, Research Triangle Park, NC, 27709, USA**
SO Abstracts of Papers, 225th ACS National Meeting, New Orleans, LA, United States, March 23-27, 2003 (2003), MEDI-268 Publisher: American Chemical Society, Washington, D. C.
CODEN: 69DSA4
DT Conference; Meeting Abstract
LA English
AB Amphipathic α-helixes are ubiquitous structural features observed in biol. active peptides. They play important roles in the folding, **protein-protein** recognition, and **protein** -membrane interaction of peptides. The **conjugation** of **amphiphilic oligomers** (polyoxyethylene alkyl ethers) to **peptide** therapeutics has been known to alter the biol. activity of the parent **peptide**. This may be due to alterations in the **protein** folding or to conformational changes in the **peptide**. In Part 2 of our study, we report results from CD Spectroscopy (CD) and Differential Scanning Calorimetry (DSC) of different insulin **conjugates**. We evaluated the effect of our **amphiphilic oligomers**, which vary in their size, sterics, and **amphiphilic** balance on the conformational changes of oral insulin **conjugates** in solution by CD. The deconvolution analyses of the **conjugates** were also performed. The thermal denaturation (Tm) of these insulin **conjugates** was determined by CD and DSC.

L107 ANSWER 12 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:184233 HCAPLUS
ED Entered STN: 11 Mar 2003
TI Effects of **amphiphilic oligomers** on oral insulin **conjugates**
AU Miller, Mark A.; Malkar, Navdeep B.; Odenbaugh, Amy L.; Surguladze, David; Danek Burgess, Krisstina S.; Bednarcik, Mark J.; Dugdell, Robert E.; Yarbrough, Kevin G.; Willie, Kirsten; **Ekwuribe, Nnochiri N.**; James, Kenneth D.
CS **Nobex Corporation, Research Triangle Park, NC, 27709, USA**
SO Abstracts of Papers, 225th ACS National Meeting, New Orleans, LA, United States, March 23-27, 2003 (2003), MEDI-267 Publisher: American Chemical Society, Washington, D. C.
CODEN: 69DSA4
DT Conference; Meeting Abstract
LA English
AB In an effort to understand the effects of **conjugating**

amphiphilic oligomers to insulin, a broad range of **oligomers**, varying in their **amphiphilicity**, length, and structure, were synthesized and **conjugated** to insulin. The physicochem. properties of the insulin **conjugates**, including in vitro and in vivo activity, were examined Part 1 of our study describes the synthesis of the **oligomers** and the activity results of the insulin **conjugates.** The in vitro assays measure agonist activity at the insulin receptor and the in vivo efficacy was assayed by oral dosing in mice. Our goal with this research is to establish a guide to generally predict the effects of **amphiphilic oligomers** not only on insulin, but on other proteins and peptides, thus facilitating the oral delivery of **protein** and **peptide conjugates.**

L107 ANSWER 13 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:946135 HCAPLUS
DN 138:16637
ED Entered STN: 13 Dec 2002
TI Preparation of growth hormone drug-polyalkylene glycol **oligomer conjugates**
IN **Ekwuribe, Nnochiri N.; Price, Christopher H.; Ansari, Aslam M.**; Odenbaugh, Amy L.
PA **Nobex Corporation, USA**
SO PCT Int. Appl., 145 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K038-27
ICS C07K001-113; C07K014-61
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 2, 3, 37
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002098452	A1	20021212	WO 2002-US17504	20020604
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003027995	A1	20030206	US 2001-873757	20010604
EP 1404361	A1	20040407	EP 2002-737344	20020604
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRAI US 2001-873757	A	20010604		
WO 2002-US17504	W	20020604		

OS MARPAT 138:16637
AB A mixture of **conjugates** in which each **conjugate** in the mixture comprises a growth hormone drug coupled to an **oligomer** that includes a polyalkylene glycol moiety is disclosed. Thus, non-polydispersed hexaethylene glycol was treated with phosgene solution, followed by treatment with N-hydroxysuccinimide (NHS) to give give the NHS ester. Human growth hormone (Saizen) was dissolved in DMSO and allowed to react with the NHS ester to give the **conjugate.**
ST polyalkylene glycol **oligomer** growth hormone **conjugate** prepn
IT Polyoxyalkylenes, biological studies
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological

study); PREP (Preparation); USES (Uses)
(**conjugates**, with growth hormone; preparation of growth hormone drug-polyalkylene glycol **oligomer conjugates**)

IT Polyoxyalkylenes, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(in alkylene glycol derivs. preparation; preparation of growth hormone drug-polyalkylene glycol **oligomer conjugates**)

IT Drug delivery systems
Molecular weight distribution
(preparation of growth hormone drug-polyalkylene glycol **oligomer conjugates**)

IT 477775-58-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(hydrogenolysis of; preparation of growth hormone drug-polyalkylene glycol **oligomer conjugates**)

IT 57-10-3, Hexadecanoic acid, reactions 75-44-5, Phosgene 112-27-6 112-35-6 112-60-7, Tetraethylene glycol 112-76-5, Octadecanoyl chloride 1679-53-4, 10-Hydroxydecanoic acid 2615-15-8 3639-35-8 5299-60-5, Ethyl 6-hydroxyhexanoate 6066-82-6, N-Hydroxysuccinimide 17696-11-6 25322-68-3, Polyethylene glycol 74124-79-1 86259-87-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(in alkylene glycol derivs. preparation; preparation of growth hormone drug-polyalkylene glycol **oligomer conjugates**)

IT 4437-01-8P, 2,5,8,11,14,17,20-Heptaoxadocosan-22-ol 9004-99-3P 29823-21-0P 51023-28-0P 62304-85-2P 70802-40-3P 74654-05-0P 87117-61-1P 105292-71-5P 124668-93-5P 477775-57-8P 477775-59-0P 477775-60-3P 477775-61-4P 477775-62-5P 477775-64-7P 477775-65-8P 477775-67-0P 477775-68-1P 477775-69-2P 477775-71-6P 477775-73-8P 477775-74-9P 477775-75-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(in alkylene glycol derivs. preparation; preparation of growth hormone drug-polyalkylene glycol **oligomer conjugates**)

IT 9004-74-4P, Monomethoxy polyethylene glycol
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(mesylation ao esterification reactions of; preparation of growth hormone drug-polyalkylene glycol **oligomer conjugates**)

IT 24342-68-5P 135649-01-3P 259228-98-3P 477775-63-6P 477775-66-9P 477775-70-5P 477775-72-7P 477775-76-1P 477775-77-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of growth hormone drug-polyalkylene glycol **oligomer conjugates**)

IT **9002-72-6DP**, Growth hormone, **conjugates** with polyalkylene glycols 12629-01-5DP, Saizen, **conjugates** with polyalkylene glycols 135649-01-3DP, **conjugates** with growth hormone 259228-98-3DP, **conjugates** with growth hormone 477775-63-6DP, **conjugates** with growth hormone 477775-66-9DP, **conjugates** with growth hormone 477775-70-5DP, **conjugates** with growth hormone 477775-72-7DP, **conjugates** with growth hormone 477775-76-1DP, **conjugates** with growth hormone 477775-77-2DP, **conjugates** with growth hormone
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of growth hormone drug-polyalkylene glycol **oligomer conjugates**)

RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Clark; US 5597797 A 1997 HCAPLUS
(2) Cunningham; US 6057292 A 2000 HCAPLUS
(3) Davis; US 4179337 A 1979 HCAPLUS

(4) Delgado; US 5349052 A 1994 HCAPLUS
(5) Ekwuribe; US 5359030 A 1994 HCAPLUS
(6) Receptagen Corporation; WO 9714740 A1 1997 HCAPLUS

L107 ANSWER 14 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:946134 HCAPLUS
DN 138:16636
ED Entered STN: 13 Dec 2002
TI Preparation of **calcitonin** drug-alkylene glycol **oligomer conjugates**
IN **Ekwuribe, Nnochiri N.**; **Price, Christopher H.**; **Ansari, Aslam M.**; Odenbaugh, Amy L.
PA **Nobex Corporation, USA**
SO PCT Int. Appl., 126 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K038-23
ICS C07K014-585
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 2, 37
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002098451	A1	20021212	WO 2002-US17575	20020604
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2003060606	A1	20030327	US 2001-873777	20010604
	US 6713452	B2	20040330		
	EP 1404360	A1	20040407	EP 2002-732030	20020604
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRAI	US 2001-873777	A	20010604		
	WO 2002-US17575	W	20020604		

OS MARPAT 138:16636
AB A mixture of **conjugates** in which each **conjugate** in the mixture comprises a **calcitonin** drug coupled to an **oligomer** that includes a polyalkylene glycol moiety is disclosed. The mixture may lower serum calcium levels in a subject by 10, 15 or ≥20%. Moreover, the mixture may be more effective at surviving an in vitro model of intestinal digestion than non-**conjugated calcitonin**. Furthermore, the mixture may exhibit a higher bioavailability than the non-**conjugated calcitonin.** Thus, non-polydispersed hexaethylene glycol was treated with phosgene solution, followed by treatment with N-hydroxysuccinimide (NHS) to give give the NHS ester. Salmon **calcitonin** was allowed to react with the NHS ester to give the **conjugate.**
ST **calcitonin** alkylene glycol **oligomer conjugate** prepn; bone **calcitonin** alkylene glycol **oligomer conjugate** prepn
IT Bone, disease
(Paget's; preparation of **calcitonin** drug-alkylene glycol **oligomer conjugates**)
IT Polyoxyalkylenes, biological studies
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological

study); PREP (Preparation); USES (Uses)
(**conjugates**, **calcitonin**; preparation of **calcitonin** drug-alkylene glycol **oligomer conjugates**)

IT Polyoxyalkylenes, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(in alkylene glycol **oligomers** preparation; preparation of **calcitonin** drug-alkylene glycol **oligomer conjugates**)

IT Bone, disease
Drug delivery systems
Molecular weight distribution
Osteoporosis
(preparation of **calcitonin** drug-alkylene glycol **oligomer conjugates**)

IT **7440-70-2**, Calcium, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(hypercalcemia; preparation of **calcitonin** drug-alkylene glycol **oligomer conjugates**)

IT 57-10-3, Palmitic acid, reactions 75-44-5, Phosgene 111-77-3 112-27-6, Triethylene glycol 112-35-6 112-60-7, Tetraethylene glycol 112-76-5, Octadecanoyl chloride 2615-15-8 5299-60-5, Ethyl 6-hydroxyhexanoate 6066-82-6, N-Hydroxysuccinimide 17696-11-6 25322-68-3, Polyethylene glycol 74124-79-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(in alkylene glycol **oligomers** preparation; preparation of **calcitonin** drug-alkylene glycol **oligomer conjugates**)

IT 1679-53-4P, 10-Hydroxydecanoic acid 3639-35-8P 4437-01-8P, 2,5,8,11,14,17,20-Heptaoxadocosan-22-ol 9004-74-4P, Monomethoxy polyethylene glycol 9004-99-3P 24342-68-5P 29823-21-0P 51023-28-0P 62304-85-2P 70802-40-3P 74654-05-0P 86259-87-2P 105292-71-5P 124668-93-5P 175172-61-9P 477775-58-9P 477775-59-0P 477775-60-3P 477775-61-4P 477775-62-5P 477775-65-8P 477775-67-0P 477775-68-1P 477775-69-2P 477775-71-6P 477775-73-8P 477775-74-9P 477775-75-0P 477775-77-2P 477781-68-3P 477781-69-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(in alkylene glycol **oligomers** preparation; preparation of **calcitonin** drug-alkylene glycol **oligomer conjugates**)

IT 135649-01-3P 259228-98-3P 477775-63-6P 477775-66-9P 477775-70-5P 477775-72-7P 477775-76-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of **calcitonin** drug-alkylene glycol **oligomer conjugates**)

IT **9007-12-9DP**, **Calcitonin**, **conjugates** with alkylene glycols 47931-85-1DP, Salmon **Calcitonin**, **conjugates** with alkylene glycols 135649-01-3DP, **conjugates** with **calcitonin** 259228-98-3DP, **conjugates** with **calcitonin** 477775-63-6DP, **conjugates** with **calcitonin** 477775-66-9DP, **conjugates** with **calcitonin** 477775-70-5DP, **conjugates** with **calcitonin** 477775-72-7DP, **conjugates** with **calcitonin** 477775-76-1DP, **conjugates** with **calcitonin** 477775-77-2DP, **conjugates** with **calcitonin**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of **calcitonin** drug-alkylene glycol **oligomer conjugates**)

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE
(1) Delgado; US 5349052 A 1994 HCAPLUS
(2) Ekwuribe, N; US 5359030 A 1994 HCAPLUS
(3) Medgenix Group S A; EP 0511903 A2 1992 HCAPLUS
(4) Receptagen Corporation; WO 9714740 A1 1997 HCAPLUS

L107 ANSWER 15 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:946130 HCAPLUS
DN 138:29120
ED Entered STN: 13 Dec 2002
TI Preparation of **peptide** drug-alkylene glycol **oligomer** **conjugates**
IN **Ekwuribe, Nnochiri N.**; **Price, Christopher H.**; **Ansari, Aslam M.**; Odenbaugh, Amy L.
PA **Nobex Corporation, USA**
SO PCT Int. Appl., 201 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K038-02
ICS A61K038-18; A61K038-19; A61K038-22; A61K038-23; A61K038-28; A61K039-385; C07K001-113; C07K002-00; C07K014-475; C07K014-52; C07K014-575; C07K014-585
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 2, 37
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002098446	A1	20021212	WO 2002-US17567	20020604
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2003228275	A1	20031211	US 2001-873797	20010604
	BR 2001006401	A	20030211	BR 2001-6401	20011011
	JP 2003104913	A2	20030409	JP 2001-317307	20011015
	EP 1404355	A1	20040407	EP 2002-737357	20020604
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRAI	US 2001-873797	A	20010604		
	WO 2002-US17567	W	20020604		

OS MARPAT 138:29120
AB A non-polydispersed mixture of **conjugates** in which each **conjugate** in the mixture comprises a **peptide** drug coupled to an **oligomer** that includes a polyalkylene glycol moiety is disclosed. The mixture may exhibit higher in vivo activity than a polydispersed mixture of similar **conjugates.** The mixture may be more effective at surviving an in vitro model of intestinal digestion than polydispersed mixts. of similar **conjugates.** The mixture may result in less inter-subject variability than polydispersed mixts. of similar **conjugates.** Thus, non-polydispersed hexaethylene glycol was treated with phosgene solution, followed by treatment with N-hydroxysuccinimide (NHS) to give give the NHS ester. Human growth hormone (Saizen) was allowed to react with the NHS ester to give the **conjugate.**
ST **peptide** drug alkylene glycol **oligomer** **conjugate** prepn

IT **Proteins**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(CART, **conjugates** with alkylene glycols; preparation of **peptide** drug-alkylene glycol **oligomer conjugates**)
IT **Proteins**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(GTP-binding, **conjugates** with alkylene glycols; preparation of **peptide** drug-alkylene glycol **oligomer conjugates**)
IT **Peptides**, biological studies
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(bag cell, **conjugates** with alkylene glycols; preparation of **peptide** drug-alkylene glycol **oligomer conjugates**)
IT **Enkephalins**
Fibronectins
Interleukins
Neurotrophic factors
Opioids
Osteocalcins
Tachykinins
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**conjugates** with alkylene glycols; preparation of **peptide** drug-alkylene glycol **oligomer conjugates**)
IT **Peptides**, biological studies
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**conjugates**, virus-related, with alkylene glycols; preparation of **peptide** drug-alkylene glycol **oligomer conjugates**)
IT Hormones, animal, biological studies
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**conjugates**, with alkylene glycol derivs.; preparation of **peptide** drug-alkylene glycol **oligomer conjugates**)
IT Growth factors, animal
Peptides, biological studies
Toxins
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**conjugates**, with alkylene glycols; preparation of **peptide** drug-alkylene glycol **oligomer conjugates**)
IT Polyoxyalkylenes, biological studies
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**conjugates**, with **peptide** drugs; preparation of **peptide** drug-alkylene glycol **oligomer conjugates**)
IT Polyoxyalkylenes, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(in alkylene glycol derivs. preparation; preparation of **peptide** drug-alkylene glycol **oligomer conjugates**)
IT Drug delivery systems
Human
Molecular weight distribution
(preparation of **peptide** drug-alkylene glycol **oligomer conjugates**)

IT Endothelin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type ETA, antagonists, **conjugates** with alkylene glycols; preparation of **peptide** drug-alkylene glycol **oligomer conjugates**)

IT Endothelin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type ETB, antagonists, **conjugates** with alkylene glycols; preparation of **peptide** drug-alkylene glycol **oligomer conjugates**)

IT Amyloid
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(β-, **conjugates** with alkylene glycols; preparation of **peptide** drug-alkylene glycol **oligomer conjugates**)

IT **50-56-6DP**, **Oxytocin**, **conjugates** with alkylene glycols 1393-25-5DP, Secretin, **conjugates** with alkylene glycols **9002-64-6DP**, PTH, **conjugates** with alkylene glycols 39362-14-6DP, **Prolactin**-releasing **peptide**, **conjugates** with alkylene glycols **82785-45-3DP**, **Neuropeptide Y**, **conjugates** with alkylene glycols 103370-86-1DP, **Parathyroid hormone**-related **peptide**, **conjugates** with alkylene glycols 106388-42-5DP, **Peptide** YY, **conjugates** with alkylene glycols 117148-67-1DP, Pancreastatin, **conjugates** with alkylene glycols 137061-48-4DP, PACAp, **conjugates** with alkylene glycols 245359-74-4DP, Orexin, **conjugates** with alkylene glycols
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**conjugates** with alkylene glycols; preparation of **peptide** drug-alkylene glycol **oligomer conjugates**)

IT 57-10-3, Palmitic acid, reactions 75-44-5, Phosgene 111-77-3 112-27-6, Triethylene glycol 112-35-6 112-76-5, Octadecanoyl chloride 1679-53-4, 10-Hydroxydecanoic acid 2615-15-8 5299-60-5, Ethyl 6-hydroxyhexanoate 6066-82-6, N-Hydroxysuccinimide 25322-68-3, Polyethylene glycol 74124-79-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(in alkylene glycol derivs. preparation; preparation of **peptide** drug-alkylene glycol **oligomer conjugates**)

IT 112-60-7P, Tetraethylene glycol 3639-35-8P 4437-01-8P, 2,5,8,11,14,17,20-Heptaoxadocosan-22-ol 9004-74-4P 9004-99-3P 17696-11-6P 24342-68-5P 29823-21-0P 62304-85-2P 70802-40-3P 74654-05-0P 86259-87-2P 105292-71-5P 124668-93-5P 142556-85-2P 175172-61-9P 477775-58-9P 477775-59-0P 477775-60-3P 477775-61-4P 477775-62-5P 477775-65-8P 477775-67-0P 477775-68-1P 477775-69-2P 477775-71-6P 477775-73-8P 477775-74-9P 477775-75-0P 477781-68-3P 477781-69-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(in alkylene glycol derivs. preparation; preparation of **peptide** drug-alkylene glycol **oligomer conjugates**)

IT 259228-98-3P 477775-63-6P 477775-66-9P 477775-70-5P 477775-72-7P 477775-76-1P 477775-77-2P 477788-13-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of **peptide** drug-alkylene glycol **oligomer conjugates**)

IT 58-82-2DP, Bradykinin, **conjugates** with alkylene glycols **1407-47-2DP**, **Angiotensin**, **conjugates** with alkylene glycols 8049-62-5DP, Zinc insulin, **conjugates** with alkylene glycols **9002-60-2DP**, ACTH, **conjugates** with alkylene glycols 9002-76-0DP, Gastrin, **conjugates** with

alkylene glycols 9002-79-3DP, Melanocyte stimulating hormone, **conjugates** with alkylene glycols 9004-10-8DP, Insulin, **conjugates** with alkylene glycols **9007-92-5DP**, **Glucagon**, **conjugates** with alkylene glycols **9011-97-6DP**, **Cholecystokinin**, **conjugates** with alkylene glycols 9015-71-8DP, Corticotropin releasing factor, **conjugates** with alkylene glycols 9015-94-5DP, Renin, **conjugates** with alkylene glycols 9034-40-6DP, LHRH, **conjugates** with alkylene glycols **11000-17-2DP**, **Vasopressin**, **conjugates** with alkylene glycols 11061-68-0DP, Human insulin, **conjugates** with alkylene glycols 12629-01-5DP, Human growth hormone, **conjugates** with alkylene glycols 24305-27-9DP, Thyrotropin-releasing hormone, **conjugates** with alkylene glycols 31362-50-2DP, Bombesin, **conjugates** with alkylene glycols 33507-63-0DP, Substance P, **conjugates** with alkylene glycols 37221-79-7DP, Vasoactiveintestinal **peptide**, **conjugates** with alkylene glycols 47931-85-1DP, Salmon **calcitonin**, **conjugates** with alkylene glycols **51110-01-1DP**, **Somatostatin**, **conjugates** with alkylene glycols **52906-92-0DP**, **Motilin**, **conjugates** with alkylene glycols 57285-09-3DP, Inhibin, **conjugates** with alkylene glycols 58391-28-9DP, Leucokinin, **conjugates** with alkylene glycols 59112-80-0DP, C-**Peptide** , **conjugates** with alkylene glycols **60118-07-2DP**, **Endorphin**, **conjugates** with alkylene glycols 72093-21-1DP, Mastoparan, **conjugates** with alkylene glycols 74135-04-9DP, Morphiceptin, **conjugates** with alkylene glycols **74913-18-1DP**, **Dynorphin**, **conjugates** with alkylene glycols 77614-16-5DP, Dermorphin, **conjugates** with alkylene glycols 83652-28-2DP, **Calcitonin** gene related **peptide**, **conjugates** with alkylene glycols 83856-13-7DP, Mast cell degranulating **peptide**, **conjugates** with alkylene glycols 85568-32-7DP, Casomorphin, **conjugates** with alkylene glycols 85637-73-6DP, Atrial natriuretic **peptide**, **conjugates** with alkylene glycols 106602-62-4DP, Amylin, **conjugates** with alkylene glycols 107666-54-6DP, GNRH associated **peptide**, **conjugates** with alkylene glycols 110119-33-0DP, Allatostatin, **conjugates** with alkylene glycols 114471-18-0DP, Brain natriuretic **peptide** , **conjugates** with alkylene glycols 116243-73-3DP, Endothelin, **conjugates** with alkylene glycols 119418-04-1DP, Galanin, **conjugates** with alkylene glycols 127830-04-0DP, C-Type natriuretic **peptide**, **conjugates** with alkylene glycols 144940-98-7DP, Guanylin, **conjugates** with alkylene glycols 154835-90-2DP, Adrenomedullin, **conjugates** with alkylene glycols 169494-85-3DP, Leptin, **conjugates** with alkylene glycols 193829-96-8DP, Cortistatin, **conjugates** with alkylene glycols 259228-98-3DP, **peptide** drug **conjugates** 477775-63-6DP, **peptide** drug **conjugates** 477775-66-9DP, **peptide** drug **conjugates** 477775-70-5DP, **peptide** drug **conjugates** 477775-72-7DP, **peptide** drug **conjugates** 477775-76-1DP, **peptide** drug **conjugates** 477775-77-2DP, **peptide** drug **conjugates** 477788-13-9DP, **peptide** drug **conjugates**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of **peptide** drug-alkylene glycol **oligomer** **conjugates**)

RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Davis; US 4179337 A 1979 HCAPLUS
(2) Delgado; US 5349052 A 1994 HCAPLUS

(3) Ekwuribe, N; US 5359030 A 1994 HCAPLUS
(4) Gilbert; US 6042822 A 2000 HCAPLUS
(5) Receptagen Corporation; WO 9714740 A1 1997 HCAPLUS
(6) Vreeland; Analytical Chemistry 2001, V73(8), P1795 HCAPLUS

L107 ANSWER 16 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:657913 HCAPLUS
DN 137:196046
ED Entered STN: 30 Aug 2002
TI Methods of treating diabetes mellitus with orally administered insulin **oligomers**
IN **Ekwuribe, Nnochiri N.**; **Price, Christopher H.**; Still, James Gordon; Filbey, Jennifer Ann
PA **Nobex Corporation, USA**; Radhakrishnan, Balasingam; Ansari, Aslam M.; Odenbaugh, Amy L.
SO PCT Int. Appl., 114 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K
CC 2-6 (Mammalian Hormones)
Section cross-reference(s): 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002065985	A2	20020829	WO 2002-US4440	20020214
	WO 2002065985	A3	20040219		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2003050228	A1	20030313	US 2002-75097	20020213
	EP 1409006	A2	20040421	EP 2002-709541	20020214
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRAI	US 2001-269198P	P	20010215		
	US 2002-347713P	P	20020111		
	WO 2002-US4440	W	20020214		

AB Methods of treating diabetes mellitus using an effective amount of an oral insulin derivative are claimed. The structure of the insulin derivative is: insulin **polypeptide**-B-Lj-Gk-R-G'm-R'-G"n-T wherein: B is a bonding moiety; L is a linker moiety; G, G' and G" are individually selected spacer moieties; R is a **lipophilic** moiety and R' is a polyalkylene glycol moiety, or R' is the **lipophilic** moiety and R is the polyalkylene glycol moiety; T is a terminating moiety; and j, k, m and n are individually 0 or 1. The structure of the insulin derivative is: insulin **polypeptide**-X(CH2)mY(C2H4O)nR, insulin **polypeptide**-X(CH2)m(OC2H4)nOR, or insulin **polypeptide** -NH-CO-(CH2)m(OC2H4)nOR, wherein: X and Y are ester moieties, thioester moieties, ether moieties, carbamate moieties, thiocarbamate moieties, carbonate moieties, thiocarbonate moieties, amide moieties, urea moieties or covalent bonds; m is between 1 and 24; n is between 1 and 50; and R is an alkyl moiety, a sugar moiety, cholesterol, adamantane, an alc. moiety, or a fatty acid moiety. A specifically claimed derivative is insulin **polypeptide**-NH-CO-(CH2)5(OC2H4)7OCH3. Formulations for capsules are exemplified.
ST diabetes mellitus treatment oral insulin **oligomer**

conjugate
IT Drug delivery systems
(capsules; methods of treating diabetes mellitus with orally administered insulin **oligomers**)
IT Diabetes mellitus
(insulin-dependent; methods of treating diabetes mellitus with orally administered insulin **oligomers**)
IT Antidiabetic agents
Diabetes mellitus
Human
(methods of treating diabetes mellitus with orally administered insulin **oligomers**)
IT 9004-10-8D, Insulin, **oligomeric conjugates**
452310-88-2D, **oligomeric conjugates** 452310-92-8D, **oligomeric conjugates** 452311-02-3D, **oligomeric conjugates** 452311-09-0D, **oligomeric conjugates** 452311-17-0D, **oligomeric conjugates** 452311-24-9D, **oligomeric conjugates** 452311-25-0D, **oligomeric conjugates** 452311-26-1D, **oligomeric conjugates** 452311-27-2D, **oligomeric conjugates** 452311-28-3D, **oligomeric conjugates** 452311-29-4D, **oligomeric conjugates** 452311-30-7D, **oligomeric conjugates** 452311-31-8D, **oligomeric conjugates** 452311-32-9D, **oligomeric conjugates** 452311-33-0D, **oligomeric conjugates** 452311-34-1D, **oligomeric conjugates** 452311-35-2D, **oligomeric conjugates** 452311-36-3D, **oligomeric conjugates** 452311-37-4D, **oligomeric conjugates** 452311-38-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods of treating diabetes mellitus with orally administered insulin **oligomers**)

L107 ANSWER 17 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:434907 HCAPLUS
DN 135:51054
ED Entered STN: 15 Jun 2001
TI **Amphiphilic** polymers **conjugates** with peptides
IN **Ekwuribe, Nnochiri N.**
PA **Nobex Corporation, USA**
SO PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K047-48
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 37
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001041812	A2	20010614	WO 2000-US33592	20001211
WO 2001041812	A3	20020321		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 6638906	B1	20031028	US 1999-459443	19991213
BR 2000016339	A	20020827	BR 2000-16339	20001211

EP 1237580 A2 20020911 EP 2000-984215 20001211
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
JP 2003516366 T2 20030513 JP 2001-543156 20001211
NO 2002002793 A 20020813 NO 2002-2793 20020612
US 2004092449 A1 20040513 US 2003-633966 20030804
PRAI US 1999-459443 A 19991213
WO 2000-US33592 W 20001211

AB Proteins and/or peptides, such as luminal **cholecystokinin** releasing factor (LCRF), are **conjugated** with **amphiphilic oligomers** and polymers. Such **conjugates** may modulate the pharmacokinetic profile of the proteins and/or peptides, thereby improving their clin. utility. Such **conjugates** may also stabilize and deliver the proteins and/or peptides, such as LCRF, to receptors in the gut without absorption into the bloodstream. **Oligomeric** carboxylic alkanols are activated with bromine and esterified. **Oligomeric** PEG is then coupled the activated alkane **oligomers.** Coupling of the PEG/alkane carboxylic acid to the free amino group of the **peptide**, is achieved with N-hydroxysuccinamide in aqueous solution at a pH where the amino group is nucleophilic. Purified **oligomers** are activated and then coupled to LCRF in variable reaction conditions that permit the attachment of **oligomers** at certain sites (N-terminus, C-terminus or K19). The compds. are purified by HPLC.

ST **amphiphilic** polymer **conjugate peptide**; **cholecystokinin** releasing factor **conjugate** pharmacokinetics

IT **Peptides**, biological studies
Proteins, general, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**amphiphilic** polymers **conjugates** with peptides)

IT Polyoxyalkylenes, biological studies
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**conjugates** with glycolipids and **cholecystokinin** releasing factor; **amphiphilic** polymers **conjugates** with peptides)

IT Intestine
(mucosa; **amphiphilic** polymers **conjugates** with peptides)

IT 9004-74-4DP, Methoxy Polyethylene glycol, **conjugates** with **cholecystokinin** releasing factor 9005-64-5DP, Polyethylene glycol sorbitan monolaurate, **conjugates** with **cholecystokinin** releasing factor 9005-65-6DP, Polyethylene glycol sorbitan monooleate, **conjugates** with **cholecystokinin** releasing factor 9005-66-7DP, Polyethylene glycol sorbitan monopalmitate, **conjugates** with **cholecystokinin** releasing factor 9005-67-8DP, Polyethylene glycol sorbitan monostearate, **conjugates** with **cholecystokinin** releasing factor 9005-69-0DP, Polyethylene glycol sorbitan trilaurate, **conjugates** with **cholecystokinin** releasing factor 9005-70-3DP, Polyethylene glycol sorbitan trioleate, **conjugates** with **cholecystokinin** releasing factor 9005-71-4DP, Polyethylene glycol sorbitan tristearate, **conjugates** with **cholecystokinin** releasing factor 9063-33-6DP, Polyethylene glycol sorbitan dioleate, **conjugates** with **cholecystokinin** releasing factor 9075-14-3DP, Polyethylene glycol sorbitan distearate, **conjugates** with **cholecystokinin** releasing factor 25322-68-3DP, Polyethylene glycol, **conjugates** with glycolipids and **cholecystokinin** releasing factor 80341-79-3DP, Polyethylene glycol sorbitan dilaurate, **conjugates** with **cholecystokinin** releasing factor

133758-44-8DP, Polyethylene glycol sorbitan dipalmitate, **conjugates** with **cholecystokinin** releasing factor
176708-20-6DP, **conjugates** with **oligomers** and polymers
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**amphiphilic** polymers **conjugates** with peptides)

L107 ANSWER 18 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:131193 HCAPLUS
DN 134:183490
ED Entered STN: 22 Feb 2001
TI **Hydrophilic** and **lipophilic** balanced microemulsion formulations of free-form and/or **conjugation**-stabilized therapeutic agents such as insulin
IN **Ekwuribe, Nnochiri Nkem**; Ramaswamy, Muthukumar; **Radhakrishnan, Balasingam**; Allaudeen, Hameedsulthan S.
PA **Protein Delivery, Inc., USA**
SO U.S., 32 pp., Cont.-in-part of U. S. 5,681,811.
CODEN: USXXAM
DT Patent
LA English
IC ICM A61K038-38
ICS C07K014-62
NCL 514003000
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 2
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6191105	B1	20010220	US 1997-958383	19971027
	US 5359030	A	19941025	US 1993-59701	19930510
	US 5438040	A	19950801	US 1994-276890	19940719
	US 5681811	A	19971028	US 1995-509422	19950731
	US 2003229006	A1	20031211	US 2003-448524	20030530
	US 2003229010	A1	20031211	US 2003-448535	20030602
PRAI	US 1993-59701	A3	19930510		
	US 1994-276890	A2	19940719		
	US 1995-509422	A2	19950731		
	US 1997-958383	A3	19971027		
	US 2000-614203	A1	20000712		

AB A therapeutic formulation comprising a microemulsion of a therapeutic agent in free and/or **conjugate** coupled form, wherein the microemulsion comprises a water-in-oil (w/o) microemulsion including a **lipophilic** phase and a **hydrophilic** phase, and has a **hydrophilic** and **lipophilic** balance (HLB) value between 3 and 7 is described. The therapeutic agent is selected from the group consisting of insulin, **calcitonin**, ACTH, **glucagon**, **somatostatin**, **somatotropin**, **somatomedin**, **parathyroid hormone**, **erythropoietin**, **hypothalamic releasing factors**, **prolactin**, **thyroid stimulating hormones**, **endorphins**, **enkephalins**, **vasopressin**, non-naturally occurring **opioids**, **superoxide dismutase**, **interferon**, **asparaginase**, **arginase**, **arginine deaminase**, adenosine deaminase, **RNase**, **trypsin**, **chymotrypsin**, **papain**, Ara-A (Arabinofuranosyladenine), acylguanosine, nordeoxyguanosine, azidothymidine, dideoxyadenosine, dideoxycytidine, dideoxyinosine, floxuridine, 6-mercaptopurine, doxorubicin, daunorubicin, or I-darubicin, erythromycin, vancomycin, oleandomycin, ampicillin, quinidine and heparin. In a particular aspect, the invention comprises an insulin composition suitable for parenteral as well as non-parenteral administration, preferably oral

or parenteral administration, comprising insulin covalently coupled with a polymer including (i) a linear polyalkylene glycol moiety and (ii) a **lipophilic** moiety, wherein the insulin, the linear polyalkylene glycol moiety and the **lipophilic** moiety are conformationally arranged in relation to one another such that the insulin in the composition has an enhanced in vivo resistance to enzymic degradation, relative to insulin alone. The microemulsion compns. of the invention are usefully employed in therapeutic as well as non-therapeutic, e.g., diagnostic, applications. For example, a microemulsion formulation was prepared containing Capmul MCM 53.0, Centrophase 31 5.7, propylene glycol 19.9, Tween 80 1.4, hexyl insulin in NaP buffer 15 mg/mL, and NaP buffer up to 100%, resp. Also, preparation of hexyl insulin **conjugates** with Me (ethylene glycol)7-O-hexanoic acid was carried out.

ST drug **conjugate** microemulsion stabilization; insulin **conjugate** microemulsion stabilization

IT Fatty acids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(C8-10, esters with propylene glycol; **hydrophilic** and **lipophilic** balanced microemulsions of free and/or **conjugated** drugs such as insulin)

IT Diagnosis
(agents; **hydrophilic** and **lipophilic** balanced microemulsions of free and/or **conjugated** drugs such as insulin)

IT Polyoxyalkylenes, biological studies
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**conjugates** with tetrahydropyran derivative and insulin; **hydrophilic** and **lipophilic** balanced microemulsions of free and/or **conjugated** drugs such as insulin)

IT Antidiabetic agents
Hydrophile-lipophile balance value
(**hydrophilic** and **lipophilic** balanced microemulsions of free and/or **conjugated** drugs such as insulin)

IT Diglycerides
Enkephalins
Glycerides, biological studies
Hypothalamic hormones
Interferons
Lecithins
Monoglycerides
Opioids
Polymers, biological studies
Polyoxyalkylenes, biological studies
Polyoxyalkylenes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**hydrophilic** and **lipophilic** balanced microemulsions of free and/or **conjugated** drugs such as insulin)

IT Drug delivery systems
(microemulsions; **hydrophilic** and **lipophilic** balanced microemulsions of free and/or **conjugated** drugs such as insulin)

IT Surfactants
(nonionic; **hydrophilic** and **lipophilic** balanced microemulsions of free and/or **conjugated** drugs such as insulin)

IT Drug delivery systems
(oral; **hydrophilic** and **lipophilic** balanced microemulsions of free and/or **conjugated** drugs such as insulin)

IT Drug delivery systems
(parenterals; **hydrophilic** and **lipophilic** balanced microemulsions of free and/or **conjugated** drugs such as

insulin)
IT Alcohols, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyhydric; **hydrophilic** and **lipophilic** balanced microemulsions of free and/or **conjugated** drugs such as insulin)
IT Fats and Glyceridic oils, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vegetable; **hydrophilic** and **lipophilic** balanced microemulsions of free and/or **conjugated** drugs such as insulin)
IT 24167-76-8, Sodium phosphide
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(buffer; **hydrophilic** and **lipophilic** balanced microemulsions of free and/or **conjugated** drugs such as insulin)
IT 102-82-9, Tri-n-butylamine 3344-77-2, 12-Bromo-1-dodecanol 7075-11-8 7693-46-1, p-Nitrophenylchloroformate 9004-74-4 9005-66-7 9005-70-3 11070-73-8, Bovine insulin 25512-65-6, Dihydropyran 161489-28-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(**hydrophilic** and **lipophilic** balanced microemulsions of free and/or **conjugated** drugs such as insulin)
IT 7075-11-8DP, tri-Bu derivative 88517-92-4P 100601-63-6P 161756-38-3P 161756-39-4P 212969-35-2P 326892-08-4P 326892-09-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(**hydrophilic** and **lipophilic** balanced microemulsions of free and/or **conjugated** drugs such as insulin)
IT 9004-95-9DP, Polyoxyethylene cetyl ether, **conjugates** with tri-Bu AraCMP 9004-99-3DP, Polyethylene glycol monostearate, **conjugates** with insulin 9005-66-7DP, **conjugates** with insulin 9005-70-3DP, **conjugates** with polysorbate trioleate 11070-73-8DP, Bovine insulin, **conjugates** 25322-68-3DP, Polyethylene glycol, **conjugates** with tetrahydropyran derivative and insulin 88517-92-4DP, **conjugates** with insulin and polyethylene glycol 212969-35-2DP, **conjugates** with hexyl insulin
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**hydrophilic** and **lipophilic** balanced microemulsions of free and/or **conjugated** drugs such as insulin)
IT 50-44-2, 6-Mercaptopurine 50-91-9, Floxuridine 56-54-2, Quinidine 57-55-6, Propylene glycol, biological studies 57-55-6D, Propylene glycol, esters 69-53-4, Ampicillin 69-65-8, D-Mannitol 114-07-8, Erythromycin 118-00-3D, Guanosine, acyl derivs., biological studies 1404-90-6, Vancomycin 1984-06-1, Sodium octanoate 3922-90-5, Oleandomycin 4097-22-7, Dideoxyadenosine 5536-17-4, Ara-A 7481-89-2, Dideoxycytidine **9000-96-8**, **Arginase 9001-73-4**
, **Papain 9001-99-4**, **RNase 9002-07-7**
, **Trypsin 9002-60-2**, ACTH, biological studies
9002-62-4, **Prolactin**, biological studies
9002-64-6, **Parathyroid hormone**
9002-71-5, **Thyroid stimulating hormone**
9002-72-6, **Somatotropin 9004-07-3**,
Chymotrypsin 9004-10-8, Insulin, biological studies 9004-10-8D, Insulin, **conjugates** with hexanoic acid derivative, biological studies 9004-10-8D, Insulin, hexyl polymer **conjugate**
, biological studies 9005-49-6, Heparin, biological studies 9005-65-6, Tween 80 **9007-12-9**, **Calcitonin 9007-92-5**,
Glucagon, biological studies **9015-68-3**,
Asparaginase 9026-93-1, Adenosine deaminase 9027-98-9
9038-70-4, **Somatomedin 9054-89-1**,
Superoxide dismutase 11000-17-2,
Vasopressin 11096-26-7, **Erythropoietin**

20830-81-3, Daunorubicin 23214-92-8, Doxorubicin 25322-68-3, Polyethylene glycol 30516-87-1, Azidothymidine **51110-01-1**, **Somatostatin** 58957-92-9, I-Darubicin **60118-07-2**, **Endorphin** 69655-05-6, Dideoxyinosine 82410-32-0 87090-08-2, Labrafil M 1944 120300-18-7, Caprol PGE 860 156259-68-6, Capmul MCM 195739-92-5, Centrophase 31
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**hydrophilic** and **lipophilic** balanced microemulsions of free and/or **conjugated** drugs such as insulin)

IT 9001-92-7, Protease
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; **hydrophilic** and **lipophilic** balanced microemulsions of free and/or **conjugated** drugs such as insulin but nor protease inhibitor)

IT 8049-47-6, Pancreatin 9001-75-6, Pepsin
RL: CAT (Catalyst use); USES (Uses)
(insulin and its **conjugates** stability in)

RE.CNT 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L107 ANSWER 19 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:911065 HCAPLUS
DN 134:76386
ED Entered STN: 29 Dec 2000
TI **Amphiphilic** drug-**oligomer conjugates** with hydrolyzable **lipophile** components and methods for making and using the same
IN **Ekwuribe, Nnochiri**; Ramaswamy, Muthukumar; Rajagopalan, Jayanthi
PA **Protein Delivery, Inc., USA**
SO PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-075
ICS A61K031-13; A61K031-16; A61K031-21; A61K031-325; A61K038-02; A61K038-28
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 2
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000078302	A1	20001228	WO 2000-US16879	20000619
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 6309633	B1	20011030	US 1999-336548	19990619
	BR 2000011772	A	20020402	BR 2000-11772	20000619
	EP 1196157	A1	20020417	EP 2000-942956	20000619
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2003502364	T2	20030121	JP 2001-504366	20000619
	ZA 2001010099	A	20030307	ZA 2001-10099	20011207
	NO 2001006143	A	20020218	NO 2001-6143	20011217
PRAI	US 1999-336548	A	19990619		
	WO 2000-US16879	W	20000619		

AB The present invention relates generally to hydrolyzable drug-**oligomer conjugates**, pharmaceutical compns. comprising such **conjugates**, and to methods for making and using such **conjugates** and pharmaceutical compns. For example, a **conjugate** of insulin, PEG, and oleic acid was prepared and can be orally administered.
ST **peptide** drug PEG **conjugate** hydrolyzable
IT **Proteins**, specific or class

RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Pituitary adenyl cyclase-activating; **amphiphilic** drug-**oligomer conjugates** with hydrolyzable **lipophile** components)

IT Drug delivery systems
Lipophilicity
(**amphiphilic** drug-**oligomer conjugates** with hydrolyzable **lipophile** components)

IT Antigens
Blood-coagulation factors
Bone morphogenetic **proteins**
Chemokines
Ciliary neurotrophic factor
Cytokines
Enkephalins
Gonadotropins
Growth factors, animal
Interferons
Interleukins
Neurotrophic factors
Peptides, biological studies
Platelet-derived growth factors
Tumor necrosis factors
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**amphiphilic** drug-**oligomer conjugates** with hydrolyzable **lipophile** components)

IT Polyoxyalkylenes, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(**amphiphilic** drug-**oligomer conjugates** with hydrolyzable **lipophile** components)

IT Neurotrophic factors
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(brain-derived; **amphiphilic** drug-**oligomer conjugates** with hydrolyzable **lipophile** components)

IT Drug delivery systems
(emulsions; **amphiphilic** drug-**oligomer conjugates** with hydrolyzable **lipophile** components)

IT Neurotrophic factors
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(glial-derived; **amphiphilic** drug-**oligomer conjugates** with hydrolyzable **lipophile** components)

IT **Proteins**, specific or class
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesis stimulating **peptide**; **amphiphilic** drug-**oligomer conjugates** with hydrolyzable **lipophile** components)

IT Thymus hormones
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thymostimulin; **amphiphilic** drug-**oligomer conjugates** with hydrolyzable **lipophile** components)

IT Transforming growth factors
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α-; **amphiphilic** drug-**oligomer conjugates** with hydrolyzable **lipophile** components)

IT Transforming growth factors
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(β-; **amphiphilic** drug-**oligomer** **conjugates** with hydrolyzable **lipophile** components)

IT **50-56-6**, **Oxytocin**, biological studies 58-82-2, Bradykinin 69-25-0, Eledoisin 1066-17-7, Colistin 1393-25-5, Secretin 1404-26-8, Polymyxin b 1405-87-4, Bacitracin 1405-97-6, Gramicidin **1407-47-2**, **Angiotensin** 1947-37-1, Tetragastrin 5534-95-2, Pentagastrin 8049-47-6, Pancreatin 9001-01-8, Kallikrein **9001-25-6**, Blood-**coagulation** **factor** VII **9001-27-8**, Factor VIII **9001-28-9**, Factor IX **9002-07-7**, **Trypsin 9002-60-2**, Adrenocorticotrophin, biological studies 9002-61-3, Human chorionic gonadotropin 9002-61-3D, Human chorionic gonadotropin, β-chain **9002-62-4**, **Prolactin**, biological studies **9002-64-6**, **Parathyroid hormone** 9002-67-9, LH 9002-69-1, Relaxin **9002-71-5**, **TSH** 9002-76-0, Gastrin 9002-79-3, MSH **9007-12-9**, **Calcitonin 9007-92-5** , **Glucagon**, biological studies **9011-97-6**, **Cholecystokinin** 9013-66-5, Glutathione peroxidase 9014-42-0, Thrombopoietin **9015-68-3**, **Asparaginase** 9015-71-8, Corticotropin-releasing factor 9015-94-5, Renin, biological studies 9034-39-3, Somatoliberin 9034-40-6, Luliberin **9038-70-4**, **Somatomedin** 9039-53-6, Urokinase **9054-89-1**, **Superoxide dismutase** 9061-61-4, Nerve growth factor 9063-57-4, Taftsin 9066-59-5, Lysozyme chloride **11000-17-2**, **Vasopressin** 11062-77-4, Superoxide 11085-36-2, Human placental lactogen **11096-26-7**, **Erythropoietin** 11128-99-7, **Angiotensin** II 12038-82-3 16679-58-6, Desmopressin **17650-98-5**, **Caerulein** 24305-27-9, TRH 25126-32-3, **Cholecystokinin**-8 (swine) 33507-63-0, Substance P 37221-79-7, Vasoactive intestinal **peptide** 37231-28-0, Melittin **39379-15-2**, **Neurotensin 51110-01-1D**, **Somatostatin**, derivs. **52906-92-0**, **Motilin** 53678-77-6, **Muramyldipeptide** 59392-49-3, Gastric inhibitory **peptide 60118-07-2**, **Endorphin** 60529-76-2, Thymopoietin 61512-21-8, Thymosin 61912-98-9, Insulin-like growth factor 62229-50-9, Epidermal growth factor 62683-29-8, CSF 63340-72-7, Thymic humoral factor 67763-96-6, Insulin-like growth factor I 67763-97-7, Insulin-like growth factor II 70904-56-2, Kyotorphin **74913-18-1**, **Dynorphin** 78922-62-0, Serum thymic factor **80043-53-4**, **Gastrin-releasing peptide** 81627-83-0, MCSF **82785-45-3**, **Neuropeptide Y** 83652-28-2, **Calcitonin** gene related **peptide** 83869-56-1, GM-CSF 85637-73-6, Atrial natriuretic **peptide** 103370-86-1, PTH-related **protein** 105250-86-0, Ebiratide 106096-92-8, Acidic fibroblast growth factor 106096-93-9, Basic fibroblast growth factor 106388-42-5, **Peptide** YY 116243-73-3, Endothelin 117148-67-1, Pancreastatin 119418-04-1, Galanin 130939-66-1, NT-3 143011-72-7, GCSF 143375-33-1, Neurotrophin 4
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**amphiphilic** drug-**oligomer** **conjugates** with hydrolyzable **lipophile** components)

IT 112-27-6, Triethylene glycol 112-77-6, Oleoyl chloride 7693-46-1, p-Nitrophenyl chloroformate 9004-10-8, Insulin, reactions 25322-68-3, Peg
RL: RCT (Reactant); RACT (Reactant or reagent)
(**amphiphilic** drug-**oligomer** **conjugates** with hydrolyzable **lipophile** components)

IT 9004-81-3P, Polyethylene glycollaurate 9004-96-0P, Polyethylene glycol oleate 10233-14-4P, Triethylene glycol oleate
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT

(Reactant or reagent)
(**amphiphilic** drug-**oligomer conjugates**
with hydrolyzable **lipophile** components)
IT 112-27-6DP, Triethylene glycol, derivs., **conjugates** with insulin
7535-00-4DP, Galactosamine, **conjugates** with PEG insulin
9004-10-8DP, Insulin, **conjugates** with PEG derivs., biological
studies 9004-81-3DP, Polyethylene glycollaurate, **conjugates**
with insulin 9004-96-0DP, Polyethylene glycol oleate, **conjugates**
with insulin 10233-14-4DP, Triethylene glycol oleate, **conjugates**
with insulin 28397-10-6DP, Octanoic acid, 2-[2-(2-
hydroxyethoxy)ethoxy]ethyl ester, **conjugates** with insulin
62304-85-2DP, Hexadecanoic acid, 2-[2-(2-hydroxyethoxy)ethoxy]ethyl ester,
conjugates with insulin
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological
study); PREP (Preparation); USES (Uses)
(**amphiphilic** drug-**oligomer conjugates**
with hydrolyzable **lipophile** components)
RE.CNT 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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(2) Buckley; US 5545618 A 1996 HCAPLUS
(3) Ekwuribe; US 5359030 A 1994 HCAPLUS
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HCAPLUS
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(7) Martinez; US 5681567 A 1997 HCAPLUS
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(9) Mill; US 4003792 A 1977 HCAPLUS
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(11) Shen; US 5907030 A 1999 HCAPLUS

L107 ANSWER 20 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:672439 HCAPLUS
DN 134:212549
ED Entered STN: 26 Sep 2000
TI Stability and physical characteristics of orally active
amphiphilic human insulin analog, methoxy (polyethylene glycol)
hexanoyl human recombinant insulin (HIM2)
AU Krishnan, B. Radha; Rajagopalan, J. S.; Burnham, J.
CS **Protein Delivery Inc., Durham, NC, 27713, USA**
SO Proceedings of the International Symposium on Controlled Release of
Bioactive Materials (2000), 27th, 1038-1039
CODEN: PCRMEY; ISSN: 1022-0178
PB Controlled Release Society, Inc.
DT Journal
LA English
CC 63-5 (Pharmaceuticals)
AB Orally active HIM2, an **amphiphilic oligomer** attached
to B29-Lys of human insulin, showed significant thermal stability in aqueous
buffer and in solid state over unmodified insulin. The change in pi value
as the result of modification at B29-Lys suggests that the dissoln. and
solubility profile of HIM2 would be different from that of insulin in the
gastrointestinal tract. The chemical modification contributed to a
concurrent increase in hydrodynamic radius of insulin but unaltered the
self-association state (monomeric) of insulin at low **protein** concentration
ST oral human insulin analog stability property; polyethylene glycol human
insulin **conjugate** stability
IT Dissolution
Self-association
(stability and phys. characteristics of orally active
amphiphilic human insulin analog, methoxy(polyethylene glycol)
hexanoyl human recombinant insulin)

IT 11061-68-0D, Human insulin, **conjugates** with methoxy(polyethylene glycol) hexanoic acid 326892-09-5D, **conjugates** with human insulin
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stability and phys. characteristics of orally active **amphiphilic** human insulin analog, methoxy(polyethylene glycol) hexanoyl human recombinant insulin)
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Radha, K; Amer Assoc Pharm Scient 1998
(2) Radha, K; Amer Assoc Pharm Scient 1999
(3) Radha, K; Proceed Int'l Symp Control Rel bioact Mater 1998, V25, P124
(4) Richard; Pharm Research 1998, V15(9), P1434
(5) Tecacs-Novak; Pharm Biomed Anal 1996, V14, P1405

L107 ANSWER 21 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:331784 HCAPLUS
ED Entered STN: 19 May 2000
TI Molecular drug delivery: Drug-polymer **conjugates** for delivery and targeting.
AU **Price, Christopher H.; Ekwuribe, Nnochiri**
CS **Protein Delivery Inc, Research Triangle Park, NC, 27709, USA**
SO Book of Abstracts, 219th ACS National Meeting, San Francisco, CA, March 26-30, 2000 (2000), MEDI-178 Publisher: American Chemical Society, Washington, D. C.
CODEN: 69CLAC
DT Conference; Meeting Abstract
LA English
AB The progression of innovations in drug delivery, applied principally to small mol. drugs, has been one of decreasing scale, from millimeter-sized "tiny-time capsules" in the 1960's to micron-sized "nanoparticles" today. Mol.-level modifications to meet drug delivery objectives are the next logical step. PDI is pioneering one approach: the covalent bonding of proprietary **amphiphilic oligomers** to specific sites on drug mols. resulting in: 1. Greater stability to enzymes and lower tendency to self-aggregate; 2. Increased cell-surface interaction to improve trans- and intra-cellular absorption; 3. Modification of pharmacokinetics to improve therapeutic ratio; 4. Targeted delivery to selected tissues; and 5. Balanced water and fat solubility for optimal formulation **Amphiphilic oligomer conjugation** has enabled the oral delivery of **protein**-based drugs: oral insulin is in Phase II clin. studies and oral **calcitonin** enters Phase I in 2000. The delivery of a CNS-active **peptide** and a small mol. drug across the blood-brain barrier has been demonstrated. A promising new area is the addition of tissue-targeting moieties to the **oligomers.**

L107 ANSWER 22 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:133428 HCAPLUS
DN 132:185416
ED Entered STN: 25 Feb 2000
TI Blood-brain barrier therapeutics
IN **Ekwuribe, Nnochiri N.; Radhakrishnan, Balasingam; Price, Christopher H.; Anderson, Wesley R., Jr.; Ausari, Aslam M.**
PA **Protein Delivery, Inc., USA**
SO PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K
CC 63-5 (Pharmaceuticals)

Section cross-reference(s): 1, **34**

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 2000009073	A2	20000224	WO 1999-US18248	19990812	
	WO 2000009073	A3	20000629			
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
	US 6703381	B1	20040309	US 1998-134803	19980814	<--
	CA 2340418	AA	20000224	CA 1999-2340418	19990812	
	AU 9956726	A1	20000306	AU 1999-56726	19990812	
	EP 1105142	A2	20010613	EP 1999-943676	19990812	
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
	BR 9914280	A	20011113	BR 1999-14280	19990812	
	JP 2002522463	T2	20020723	JP 2000-564577	19990812	
	US 2004102381	A1	20040527	US 2003-716578	20031119	<--
	US 2004110735	A1	20040610	US 2003-716975	20031119	
PRAI	US 1998-134803	A	19980814			
	WO 1999-US18248	W	19990812			

AB The present invention relates to **amphiphilic** drug-**oligomer conjugates** capable of traversing the blood-brain barrier and to methods of making and using such **conjugates**. **Amphiphilic** drug-**oligomer conjugates** comprise a therapeutic compound **conjugated** to an **oligomer**, wherein the **oligomer** comprises a **lipophilic** moiety coupled to a **hydrophilic** moiety. The **conjugates** of the invention further comprise therapeutic agents such as proteins, peptides, nucleosides, nucleotides, antiviral agents, antineoplastic agents, antibiotics, etc., and prodrugs, precursors, derivs. and intermediates thereof, chemical coupled to **amphiphilic oligomers**. One example **conjugate** prepared was **Met -enkephalin** with a succinimidyl triethylene glycol monohexadecyl ester derivative

ST blood brain barrier **conjugate peptide oligomer**

IT **Enkephalins**
RL: RCT (Reactant); RACT (Reactant or reagent)
(analogs; blood-brain barrier therapeutics comprising drug-**oligomer conjugates**)

IT Blood-brain barrier
(blood-brain barrier therapeutics comprising drug-**oligomer conjugates**)

IT **Antibodies**
Blood-coagulation factors
CD4 (antigen)
Hemoglobins
Hypothalamic hormones
Interferons
Opioids
Peptides, biological studies
Proteins, general, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(blood-brain barrier therapeutics comprising drug-**oligomer conjugates**)

IT 9004-10-8DP, Insulin, **conjugates** with polyoxyalkylene derivative, biological studies 259229-23-7DP, **conjugates** with peptides
RL: BPR (Biological process); BSU (Biological study, unclassified); SPN

(Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(blood-brain barrier therapeutics comprising drug-**oligomer conjugates**)

IT **57-88-5**, **Cholesterol**, reactions 111-46-6, reactions 112-27-6, Triethylene glycol 112-82-3 623-65-4, Palmitic anhydride 4484-59-7, Triethylene glycol monohexadecyl ether 6066-82-6, Hydroxysuccinimide 13887-98-4, 3,6,9-Trioxaundecanedioic acid **58569-55-4**, **Met-enkephalin** 74124-79-1, N,N'-Disuccinimidyl carbonate
RL: RCT (Reactant); RACT (Reactant or reagent)
(blood-brain barrier therapeutics comprising drug-**oligomer conjugates**)

IT 5274-61-3P 31255-25-1P 62304-85-2P, Triethylene glycol monohexadecanoate 259228-98-3P 259228-99-4P 259229-23-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(blood-brain barrier therapeutics comprising drug-**oligomer conjugates**)

IT 4484-59-7DP, **conjugates** with **enkephalin** 5274-61-3DP, **conjugates** with **enkephalin** 62304-85-2DP, **conjugates** with **enkephalin** 259229-00-0P 259229-01-1DP, **conjugates** with **enkephalin** 259229-02-2DP, **conjugates** with **enkephalin**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(blood-brain barrier therapeutics comprising drug-**oligomer conjugates**)

IT **50-56-6**, **Oxytocin**, biological studies 74-79-3, Arginine, biological studies **1407-47-2**, **Angiotensin** **9000-96-8**, **Arginase** **9001-73-4**, **Papain** **9001-78-9** **9001-99-4**, **Ribonuclease** **9002-07-7**, **Trypsin** **9002-60-2**, **Adrenocorticotropic hormone**, biological studies **9002-62-4**, **Prolactin**, biological studies **9002-64-6**, **Parathyroid hormone** **9002-71-5**, **Thyroid stimulating hormone** **9002-72-6**, **Somatotropin** **9004-07-3**, **Chymotrypsin** **9007-12-9**, **Calcitonin** **9007-92-5**, **Glucagon**, biological studies **9011-97-6**, **Cholecystokinin** **9015-68-3**, **Asparaginase** **9026-93-1**, **Adenosine deaminase** **9038-70-4**, **Somatomedin** **9054-89-1**, **Superoxide dismutase** **11000-17-2**, **Vasopressin** **11096-26-7**, **Erythropoietin** **17650-98-5**, **Caerulein** **39379-15-2**, **Neurotensin** **51110-01-1**, **Somatostatin** **52906-92-0**, **Motilin** **60118-07-2**, **Endorphin** **74913-18-1**, **Dynorphin** **80043-53-4**, **Gastrin-releasing peptide** **82785-45-3**, **Neuropeptide Y** **85916-47-8**, **Katacalcin** (human) **139639-23-9**, **Tissue plasminogen activator** **259229-03-3** **259229-04-4** **259229-05-5** **259229-06-6** **259229-07-7** **259229-08-8**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(blood-brain barrier therapeutics comprising drug-**oligomer conjugates**)

L107 ANSWER 23 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:722185 HCAPLUS
DN 132:284008

ED Entered STN: 12 Nov 1999
TI Oral delivery of **calcitonin** by **conjugation** with **amphiphilic oligomers**
AU Radha Krishnan, B.; Ramaswamy, M.; Rajagopalan, J. S.; **Anderson, W. R.**; Allaudeen, H. S.; Myung, S.; **Ekwuribe, N.**
CS **Protein Delivery Inc., Durham, NC, 27713, USA**
SO Proceedings of the International Symposium on Controlled Release of Bioactive Materials (1999), 26th, 149-150
CODEN: PCRMEY; ISSN: 1022-0178
PB Controlled Release Society, Inc.
DT Journal
LA English
CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 2
AB **Calcitonin** was modified with a dodecyl PEG derivative to introduce **amphiphilic** properties and increased enzyme stability. The properties increased the oral activity of **calcitonin.** Modification at ≥1 of the Lys residues did not affect biol. activity.
ST **calcitonin amphiphilic oligomer conjugate** oral delivery
IT **Amphiphiles**
Drug bioavailability
(oral delivery of **calcitonin** by **conjugation** with **amphiphilic oligomers**)
IT Drug delivery systems
(oral; oral delivery of **calcitonin** by **conjugation** with **amphiphilic oligomers**)
IT 263759-19-9DP, reaction products with **calcitonin**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(oral delivery of **calcitonin** by **conjugation** with **amphiphilic oligomers**)
IT **9007-12-9DP, Calcitonin, conjugates** with PEG derivative
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(oral delivery of **calcitonin** by **conjugation** with **amphiphilic oligomers**)
IT 9004-74-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(oral delivery of **calcitonin** by **conjugation** with **amphiphilic oligomers**)
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Deftos, L; The Calcitonins 1989, V3, P67
(2) Nesbitt, T; Amer Soc Bone and Mineral Res 1998
(3) Radha Krishnan, B; Proceed Int'l Symp Control Rel Bioact Mater 1998, V25, P124

L107 ANSWER 24 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:701459 HCAPLUS
DN 128:26913
ED Entered STN: 07 Nov 1997
TI **Conjugation**-stabilized therapeutic agent compositions, delivery and diagnostic formulations comprising same, and method of making and using the same
IN **Ekwuribe, Nnochiri Nkem**
PA **Protein Delivery, Inc., USA**
SO U.S., 23 pp., Cont.-in-part of U.S. 5,438,040.

CODEN: USXXAM
DT Patent
LA English
IC ICM A61K037-16
NCL 514008000
CC 63-6 (Pharmaceuticals)
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5681811	A	19971028	US 1995-509422	19950731
	US 5359030	A	19941025	US 1993-59701	19930510
	US 5438040	A	19950801	US 1994-276890	19940719
	CA 2227891	AA	19970213	CA 1996-2227891	19960729
	WO 9704796	A1	19970213	WO 1996-US12425	19960729
	W: AU, CA, CN, IL, JP, MX				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9666409	A1	19970226	AU 1996-66409	19960729
	AU 698944	B2	19981112		
	EP 841936	A1	19980520	EP 1996-926169	19960729
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	CN 1192690	A	19980909	CN 1996-196079	19960729
	JP 11511131	T2	19990928	JP 1996-507838	19960729
	US 6191105	B1	20010220	US 1997-958383	19971027
	US 2003229006	A1	20031211	US 2003-448524	20030530
	US 2003229010	A1	20031211	US 2003-448535	20030602
PRAI	US 1993-59701	A3	19930510		
	US 1994-276890	A2	19940719		
	US 1995-509422	A	19950731		
	WO 1996-US12425	W	19960729		
	US 1997-958383	A3	19971027		
	US 2000-614203	A1	20000712		

AB A stabilized **conjugated** therapeutic agent complex comprising a therapeutic agent **conjugatively** coupled to a polymer including **lipophilic** and **hydrophilic** moieties, wherein the therapeutic agent may for example be selected from the group consisting of insulin, **calcitonin**, ACTH, **glucagon**, **somatostatin**, **somatotropin**, **somatomedin**, **parathyroid hormone**, **erythropoietin**, **hypothalamic releasing factors**, **prolactin**, **thyroid stimulating hormones**, **endorphins**, **enkephalins**, **vasopressin**, non-naturally occurring **opioids**, **superoxide dismutase**, **interferon**, **asparaginase**, **arginase**, **arginine deaminase**, adenosine deaminase, **RNase**, **trypsin**, **chymotrypsin**, **papain**, Ara-A (Arabinofuranosyladenine), Acylguanosine, Nordeoxyguanosine, Azidothymidine, Dideoxyadenosine, Dideoxycytidine, Dideoxyinosine Floxuridine, 6-Mercaptopurine, Doxorubicin, Daunorubicin, or Idarubicin, Erythromycin, Vancomycin, oleandomycin, Ampicillin; Quinidine and Heparin. In a particular aspect, the invention comprises an insulin composition suitable for parenteral as well as non-parenteral administration, preferably oral or parenteral administration, comprising insulin covalently coupled with a polymer including (i) a linear polyalkylene glycol moiety and (ii) a **lipophilic** moiety, wherein the insulin, the linear polyalkylene glycol moiety and the **lipophilic** moiety are conformationally arranged in relation to one another such that the insulin in the composition has an enhanced in vivo resistance to enzymic degradation, relative to insulin alone. One, two, or three polymer constituents may be covalently attached to the therapeutic agent mol., with one polymer constituent being preferred. The **conjugates** of the invention are usefully employed in therapeutic as well as non-therapeutic, e.g., diagnostic,

applications, and the therapeutic agent and polymer may be covalently coupled to one another, or alternatively may be associatively coupled to one another, e.g., by hydrogen bonding or other associative bonding relationship.

ST drug polymer **conjugate** stabilized

IT Haptens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**conjugates**, with **antibodies**; **conjugation**-stabilized therapeutic agent compns., delivery and diagnostic formulations)

IT **Antibodies**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**conjugates**, with haptens; **conjugation**-stabilized therapeutic agent compns., delivery and diagnostic formulations)

IT Antitumor agents
Drug delivery systems
(**conjugation**-stabilized therapeutic agent compns., delivery and diagnostic formulations)

IT Polyoxyalkylenes, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(**conjugation**-stabilized therapeutic agent compns., delivery and diagnostic formulations)

IT Antiarrhythmics
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**conjugation**-stabilized therapeutic agent compns., delivery and diagnostic formulations)

IT **Antibodies**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**conjugation**-stabilized therapeutic agent compns., delivery and diagnostic formulations)

IT Anticoagulants
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**conjugation**-stabilized therapeutic agent compns., delivery and diagnostic formulations)

IT **Blood-coagulation factors**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**conjugation**-stabilized therapeutic agent compns., delivery and diagnostic formulations)

IT Growth factors, animal
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**conjugation**-stabilized therapeutic agent compns., delivery and diagnostic formulations)

IT Hormones, animal, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**conjugation**-stabilized therapeutic agent compns., delivery and diagnostic formulations)

IT **Interferons**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**conjugation**-stabilized therapeutic agent compns., delivery and diagnostic formulations)

IT Nucleosides, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**conjugation**-stabilized therapeutic agent compns., delivery and diagnostic formulations)

IT Nucleotides, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**conjugation**-stabilized therapeutic agent compns., delivery and diagnostic formulations)

IT **Opioids**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**conjugation**-stabilized therapeutic agent compns., delivery and diagnostic formulations)

IT **Peptides**, biological studies

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**conjugation**-stabilized therapeutic agent compns., delivery and diagnostic formulations)

IT **Proteins**, general, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**conjugation**-stabilized therapeutic agent compns., delivery and diagnostic formulations)

IT Epitopes
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(viral; **conjugation**-stabilized therapeutic agent compns., delivery and diagnostic formulations)

IT 3344-77-2, 12-Bromo-1-dodecanol 7075-11-8 7693-46-1, p-Nitrophenyl chloroformate 9005-66-7 25322-68-3 25512-65-6, Dihydropyran 26266-58-0
RL: RCT (Reactant); RACT (Reactant or reagent)
(**conjugation**-stabilized therapeutic agent compns., delivery and diagnostic formulations)

IT 9004-99-3P, Polyethylene glycol monostearate 88517-92-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(**conjugation**-stabilized therapeutic agent compns., delivery and diagnostic formulations)

IT **9001-78-9DP**, **conjugates** with polymers 9004-10-8DP, Insulin, **conjugates** with polymers, biological studies 9004-95-9DP, Polyoxyethylene cetyl ether, reaction products with Ara-CMP derivative 65139-86-8DP, **conjugates** with polymers 161756-38-3DP, reaction products with insulin 161756-39-4DP, reaction products with insulin
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**conjugation**-stabilized therapeutic agent compns., delivery and diagnostic formulations)

IT 50-44-2, 6-Mercaptopurine 50-91-9, Floxuridine 56-54-2, Quinidine 69-53-4, Ampicillin 114-07-8, Erythromycin 118-00-3D, Guanosine, acyl derivs., biological studies 1404-90-6, Vancomycin 3922-90-5, Oleandomycin 4097-22-7, Dideoxyadenosine 5536-17-4, Ara-A 7481-89-2, Dideoxycytidine **9000-96-8**, **Arginase 9001-73-4**, **Papain 9001-99-4**, **Ribonuclease 9002-07-7**, **Trypsin 9002-62-4**, **Prolactin**, biological studies **9002-64-6**, **Parathyroid hormone 9002-71-5**, **Thyroid stimulating hormone 9002-72-6**, **Somatotropin 9004-07-3**, **Chymotrypsin** 9005-49-6, Heparin, biological studies **9007-12-9**, **Calcitonin 9007-92-5**, **Glucagon**, biological studies **9015-68-3**, **Asparaginase 9026-93-1**, Adenosine deaminase 9027-98-9 **9038-70-4**, **Somatomedin 9054-89-1**, **Superoxide dismutase 11000-17-2**, **Vasopressin 11096-26-7**, **Erythropoietin** 20830-81-3, Daunorubicin 23214-92-8, Doxorubicin 30516-87-1, Azidothymidine **51110-01-1**, **Somatostatin** 58957-92-9, Idarubicin **60118-07-2**, **Endorphin** 69655-05-6, Dideoxyinosine 82410-32-0 **139639-23-9**, **Tissue plasminogen activator**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**conjugation**-stabilized therapeutic agent compns., delivery and diagnostic formulations)

L107 ANSWER 25 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:224085 HCAPLUS
DN 126:216681
ED Entered STN: 07 Apr 1997

TI **Conjugation**-stabilized therapeutic agent compositions, delivery and diagnostic formulations
IN **Ekwuribe, Nnochiri Nkem**
PA **Protein Delivery, Inc., USA**
SO PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K038-16
CC 63-6 (Pharmaceuticals)
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9704796	A1	19970213	WO 1996-US12425	19960729
	W: AU, CA, CN, IL, JP, MX				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 5681811	A	19971028	US 1995-509422	19950731
	AU 9666409	A1	19970226	AU 1996-66409	19960729
	AU 698944	B2	19981112		
	EP 841936	A1	19980520	EP 1996-926169	19960729
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 11511131	T2	19990928	JP 1996-507838	19960729
PRAI	US 1995-509422	A	19950731		
	US 1993-59701	A3	19930510		
	US 1994-276890	A2	19940719		
	WO 1996-US12425	W	19960729		

AB A stabilized **conjugated** therapeutic agent complex comprising a therapeutic agent **conjugatively** coupled to a polymer including **lipophilic** and **hydrophilic** moieties. In a particular aspect, the invention comprises an insulin composition suitable for parenteral as well as non-parenteral administration, preferably oral or parenteral administration, comprising insulin covalently coupled with a polymer including: (i) a linear polyalkylene glycol moiety and (ii) a **lipophilic** moiety, wherein the insulin, the linear polyalkylene glycol moiety and the **lipophilic** moiety are conformationally arranged in relation to one another such that the insulin in the composition has enhanced in vivo resistance to enzymic degradation, relative to insulin alone. One, two, or three polymer constituents may be covalently attached to the therapeutic agent mol., with one polymer constituent being preferred. The **conjugates** of the invention are usefully employed in therapeutic as well as non-therapeutic, e.g., diagnostic, applications, and the therapeutic agent and polymer may be covalently coupled to one another, or alternatively may be associatively coupled to one another, e.g., by hydrogen bonding or other associative bonding relationship.

ST insulin **conjugate** drug delivery diagnostic; polymer insulin **conjugate**

IT Diagnosis
(agents; **conjugation**-stabilized therapeutic agent compns., delivery and diagnostic formulations)

IT Antitumor agents
Drug delivery systems
(**conjugation**-stabilized therapeutic agent compns., delivery and diagnostic formulations)

IT Polyoxyalkylenes, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(**conjugation**-stabilized therapeutic agent compns., delivery and diagnostic formulations)

IT Nucleosides, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**conjugation**-stabilized therapeutic agent compns., delivery and diagnostic formulations)

IT **Peptides**, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**conjugation**-stabilized therapeutic agent compns., delivery and diagnostic formulations)
IT 3344-77-2, 12-Bromo-1-dodecanol 7693-46-1, p-Nitrophenyl chloroformate 9004-99-3, Polyethylene glycol monostearate 9005-66-7 9005-70-3 25322-68-3 25512-65-6, Dihydropyran
RL: RCT (Reactant); RACT (Reactant or reagent)
(**conjugation**-stabilized therapeutic agent compns., delivery and diagnostic formulations)
IT 9004-10-8DP, Insulin, **conjugates** with polyol polymers, preparation 88517-92-4P 161756-38-3P 161756-39-4P 188023-85-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(**conjugation**-stabilized therapeutic agent compns., delivery and diagnostic formulations)
IT 161756-38-3DP, **conjugates** with insulin 161756-39-4DP, **conjugates** with insulin
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**conjugation**-stabilized therapeutic agent compns., delivery and diagnostic formulations)

L107 ANSWER 26 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:227625 HCAPLUS
DN 122:196973
ED Entered STN: 06 Dec 1994
TI **Conjugation**-stabilized **polypeptide** compositions, therapeutic delivery and diagnostic formulations comprising same, and method of making and using the same
IN **Ekwuribe, Nnochiri N.**
PA **Protein Delivery, Inc., USA**
SO U.S., 22 pp.
CODEN: USXXAM
DT Patent
LA English
IC ICM C07K007-40
ICS C07K007-36; C07K017-08; C08H001-00
NCL 530303000
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 9, **34**
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5359030	A	19941025	US 1993-59701	19930510
	CA 2162366	AA	19941124	CA 1994-2162366	19940510
	WO 9426778	A1	19941124	WO 1994-US5204	19940510
	W: AU, CA, JP				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9469466	A1	19941212	AU 1994-69466	19940510
	AU 694919	B2	19980806		
	EP 707596	A1	19960424	EP 1994-917946	19940510
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	JP 08510255	T2	19961029	JP 1994-525657	19940510
	EP 1264837	A1	20021211	EP 2002-77075	19940510
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
	JP 2003160598	A2	20030603	JP 2002-260459	19940510
	JP 2003206236	A2	20030722	JP 2002-260460	19940510
	IL 109619	A1	20001206	IL 1994-109619	19940511
	US 5438040	A	19950801	US 1994-276890	19940719
	CN 1120457	A	19960417	CN 1994-117233	19941014
	CN 1080575	B	20020313		
	US 5681811	A	19971028	US 1995-509422	19950731

	US 6191105	B1	20010220	US 1997-958383	19971027
	US 2003229006	A1	20031211	US 2003-448524	20030530
	US 2003229010	A1	20031211	US 2003-448535	20030602
PRAI	US 1993-59701	A	19930510		
	EP 1994-917946	A3	19940510		
	JP 1994-525657	A3	19940510		
	WO 1994-US5204	W	19940510		
	US 1994-276890	A2	19940719		
	US 1995-509422	A2	19950731		
	US 1997-958383	A3	19971027		
	US 2000-614203	A1	20000712		

AB A stabilized **conjugated peptide** complex comprising a **peptide conjugatively** coupled to a polymer including **lipophilic** and **hydrophilic** moieties, wherein the **peptide** may for example be selected from the group consisting of insulin, **calcitonin**, ACTH, **glucagon**, **somatostatin**, **somatotropin**, **somatomedin**, **parathyroid hormone**, **erythropoietin**, **hypothalamic releasing factors**, **prolactin**, **thyroid stimulating hormones**, **endorphins**, **enkephalins**, **vasopressin**, non-naturally occurring **opioids**, **superoxide dismutase**, **interferon**, **asparaginase**, **arginase**, **arginine deaminase**, adenosine deaminase, **RNase**, **trypsin**, **chymotrypsin**, and **papain**. In a particular aspect, the invention comprises an insulin composition suitable for parenteral as well as non-parenteral administration, preferably oral or parenteral administration, comprising insulin covalently coupled with a polymer including (i) a linear polyalkylene glycol moiety and (ii) a **lipophilic** moiety, wherein the insulin, the linear polyalkylene glycol moiety and the **lipophilic** moiety are conformationally arranged in relation to one another such that the insulin in the composition has an enhanced in vivo resistance to enzymic degradation, relative to insulin alone. One, two, or three polymer constituents may be covalently attached to the insulin mol., with one polymer constituent being preferred. The **conjugates** of the invention are usefully employed in therapeutic as well as non-therapeutic, e.g., diagnostic, applications, and the **peptide** and polymer may be covalently coupled to one another, or alternatively may be associatively coupled to one another, e.g., by hydrogen bonding or other associative bonding relationship.

ST **peptide conjugate** polymer diagnosis therapeutic

IT Diagnosis
Therapeutics
(**conjugation**-stabilized **polypeptide** compns., therapeutic delivery and diagnostic formulations)

IT **Enkephalins**
Interferons
Opioids
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(reaction products, with polymers; **conjugation**-stabilized **polypeptide** compns., therapeutic delivery and diagnostic formulations)

IT **Peptides**, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(reaction products, with polymers; **conjugation**-stabilized **polypeptide** compns., therapeutic delivery and diagnostic formulations)

IT 3344-77-2, 12-Bromo-1-dodecanol 7693-46-1, p-Nitrophenyl chloro formate 9004-99-3, Polyethylene glycol monostearate 9005-66-7 9005-70-3 25322-68-3, Peg
RL: RCT (Reactant); RACT (Reactant or reagent)
(**conjugation**-stabilized **polypeptide** compns.,

therapeutic delivery and diagnostic formulations)
IT 88517-92-4DP, reaction products with polyethylene glycol and with peptides
88517-92-4P 159561-03-2P 161756-38-3P 161756-39-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(**conjugation**-stabilized **polypeptide** compns.,
therapeutic delivery and diagnostic formulations)
IT **9001-78-9DP**, reaction products with polymers 9004-10-8DP,
Insulin, reaction products with polysorbate derivs. 25322-68-3DP, Peg,
derivs., reaction products with peptides 159561-03-2DP, reaction
products with peptides 161756-38-3DP, reaction products with peptides
161756-39-4DP, reaction products with peptides
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**conjugation**-stabilized **polypeptide** compns.,
therapeutic delivery and diagnostic formulations)
IT **9000-96-8D**, **Arginase**, reaction products with polymers
9001-73-4D, **Papain**, reaction products with polymers
9001-99-4D, **RNase**, reaction products with polymers
9002-07-7D, **Trypsin**, reaction products with polymers
9002-60-2D, ACTH, reaction products with polymers
9002-62-4D, **Prolactin**, reaction products with polymers
9002-72-6D, **Somatotropin**, reaction products with
polymers **9004-07-3D**, **Chymotrypsin**, reaction products
with polymers **9007-12-9D**, **Calcitonin**, reaction
products with polymers **9007-92-5D**, **Glucagon**, reaction
products with polymers **9015-68-3D**, **Asparaginase**,
reaction products with polymers **9026-93-1D**, Adenosine deaminase,
reaction products with polymers 9027-98-9D, reaction products with
polymers **9038-70-4D**, **Somatomedin**, reaction products
with polymers **9054-89-1D**, **Superoxide dismutase**
, reaction products with polymers **11000-17-2**,
Vasopressin 11096-26-7D, **Erythropoietin**,
reaction products with polymers **51110-01-1D**,
Somatostatin, reaction products with polymers
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**conjugation**-stabilized **polypeptide** compns.,
therapeutic delivery and diagnostic formulations)
IT **60118-07-2**, **Endorphin**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(reaction products with polymers; **conjugation**-stabilized **polypeptide** compns., therapeutic delivery and diagnostic formulations)
IT **9002-64-6**, **Parathyroid hormone**
9002-71-5, **TSH**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(reaction products, with polymers; **conjugation**-stabilized **polypeptide** compns., therapeutic delivery and diagnostic formulations)

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FILE 'WPIX' ENTERED AT 08:51:35 ON 06 JUL 2004
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FILE LAST UPDATED: 2 JUL 2004 <20040702/UP>
MOST RECENT DERWENT UPDATE: 200442 <200442/DW>
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L115 ANSWER 1 OF 21 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2004-178651 [17] WPIX
CR 1994-341060 [42]; 1995-274901 [36]; 1997-145369 [13]; 2001-373408 [39];
2004-178652 [17]
DNC C2004-070709
TI New **amphiphilic oligomers** useful for modification of
characteristics of a drug, for changing e.g. solubility, biocompatibility
or biodegradation properties.
DC A96 B04 B05 D16
IN EKWURIBE, N N
PA (EKWU-I) EKWURIBE N N
CYC 1
PI US 2003229006 A1 20031211 (200417)* 31 A61K038-16 <--
ADT US 2003229006 A1 Div ex US 1993-59701 19930510, CIP of US 1994-276890
19940719, CIP of US 1995-509422 19950731, Div ex US 1997-958383 19971027,
Cont of US 2000-614203 20000712, US 2003-448524 20030530
FDT US 2003229006 A1 Div ex US 5359030, CIP of US 5438040, CIP of US 5681811,
Div ex US 6191105
PRAI US 1997-958383 19971027; US 1993-59701 19930510;
US 1994-276890 19940719; US 1995-509422 19950731;
US 2000-614203 20000712; US 2003-448524 20030530
IC ICM **A61K038-16**
ICS C07C059-10; C07C271-08; **C07K014-435**
AB US2003229006 A UPAB: 20040310
NOVELTY - **Amphiphilic oligomers** useful for
modification of characteristics of a drug, for changing e.g. solubility,
biocompatibility or biodegradation properties, are new.
DETAILED DESCRIPTION - **Amphiphilic oligomers** of
formula (II), their salts, activated form, or N-hydroxy-succinimide esters
are new.
A-(CH2)m-(OC2H4)n-XR (I) and A-(OC2H4)n-XR (II)
A = -C(O)ONH2, -C(O)OH or -NH-C(O)OH;
m = 2 - 15;
n = 5 - 120;
X = -O-, -S-, -C(O)O- or -C(O)NH-; and
R = alkyl.
INDEPENDENT CLAIMS are included for:
(1) a branched **oligomer** comprising (I) or (II); and

(2) a protein or peptide covalently coupled to (I) or (II).
USE - For modifying pharmaceutical characteristics of a drug (claimed), e.g. solubility, biocompatibility or biodegradation.
ADVANTAGE - The drug **conjugated** with **oligomer** has enhanced in vivo resistance to enzymatic degradation, improved solubility, stability, high degree of biocompatibility, are non-toxic, non-antigenic, non-immunogenic, do not interfere with biological activities of enzymes and are easily excreted from living organisms relative to the **unconjugated** form devoid of the **oligomer.**
Dwg.0/6
FS CPI
FA AB; DCN
MC CPI: A10-E01; A12-V01; B04-C01; B04-C03C; B04-N04; B10-A11B; B10-A12C; B10-A18; B10-C04D; D05-C
TECH UPTX: 20040310
TECHNOLOGY FOCUS - POLYMERS - Preparation: Preparation of (I) (where A is -C(O)OH) involves reacting bromo fatty acid ethyl ester of formula CH3CH2OC(O)-(CH2)m-Br (Ib) with polyethylene glycol derivative of formula HOCH2CH2-(OC2H4)n-XR (Ic) in the presence of sodium hydride followed by deprotection of the resultant ester by dilute acid or base.
ABEX UPTX: 20040310
SPECIFIC COMPOUNDS - Methyl(ethyleneglycol)7-O-hexanoic acid is specifically claimed as the **oligomer.**

EXAMPLE - To a solution of methyl(ethyleneglycol)7-OH (25 g) in dry tetrahydrofuran (THF) (52 ml) was added a suspension of sodium hydride (NaH) (3.057 g) in dry THF (71 ml) at less than 20 degreesC. The resulting solution was stirred for 3 hours and 1-bromoethyl hexanoate (15.93 g) in THF (20 ml) was added. The resulting solution was stirred for 6 - 8 hours and after work up methyl(ethyleneglycol)7-O-ethyl hexanoate (A) was obtained. (A) (25 g) was stirred with NaOH (76.21 ml) at room temperature for 3 hours. Acidification with HCl followed by purification yielded methyl(ethyleneglycol)7-O-hexanoic acid.

DEFINITIONS - Preferred Definitions: Preferably in (II):
X = O; and
R = methyl.

L115 ANSWER 2 OF 21 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2004-090737 [09] WPIX
DNC C2004-036868
TI Use of an insulin polypeptide-**oligomer conjugate** for reducing hypoglycemic episodes for treating diabetes mellitus.
DC B04
IN KOSUTIC, G; STILL, J G
PA (KOSU-I) KOSUTIC G; (STIL-I) STILL J G; (NOBE-N) NOBEX CORP
CYC 103
PI WO 2003105768 A2 20031224 (200409)* EN 56 A61K000-00
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
US 2004038867 A1 20040226 (200416) A61K038-28 <--
ADT WO 2003105768 A2 WO 2003-US18763 20030613; US 2004038867 A1 Provisional US 2002-388988P 20020613, US 2003-461199 20030613
PRAI US 2002-388988P 20020613; US 2003-461199 20030613
IC ICM A61K000-00; **A61K038-28**
AB WO2003105768 A UPAB: 20040205
NOVELTY - Reduction of hypoglycemic episodes for treating diabetes mellitus involves orally administering an insulin polypeptide-

oligomer conjugate (a). (a) comprises a **hydrophilic** moiety and a **lipophilic** moiety.

ACTIVITY - Antidiabetic.

MECHANISM OF ACTION - None given.

USE - For treating diabetes mellitus by reducing hypoglycemic episodes (claimed).

ADVANTAGE - (a) reduces the number and/or severity of hypoglycemic episodes experienced by the subject during a given time period when compared with the number and/or severity of hypoglycemic episodes that would have been experienced during a similar time period by the subject in a control group parenterally administered insulin or an insulin analog in an amount that provides a substantially equivalent level of glycemic control. The method provides tight control of blood glucose in a patient having end-stage kidney disease and has severe vision loss as a complication resulting from diabetes mellitus.

Dwg.0/2

FS CPI

FA AB; DCN

MC CPI: B04-J03A; B04-N02; B14-S04

TECH UPTX: 20040205

TECHNOLOGY FOCUS - POLYMERS - Preferred **Conjugate**: (a) comprises a lysine at B-29, an A chain having an N terminus, and a B chain having an N terminus (where the **oligomer** of (a) is coupled to lysine at B-29, N terminus of the A chain, and N terminus of the B chain; preferably coupled to lysine at B-29). (a) is present as a monodispersed mixture. Preferred Components: The **hydrophilic** moiety is a polyalkylene glycol moiety. The **lipophilic** moiety is an alkyl or fatty acid moiety. (a) comprises a compound of formulae Insulin Polypeptide-B-Lj-Gk-R-G'm-R'-Gn-T (I) or Insulin Polypeptide-NH-C(O)-(CH2)5(OC2H4)7OCH3 (II).

B = bonding moiety;

L = linker moiety;

G, G' and G = spacer moieties;

R and R' = **lipophilic** moiety or polyalkylene glycol moiety;

T = terminating moiety; and

j, k, m and n = 0 or 1.

Provided that when one of R or R' is **lipophilic** moiety, then the other is polyalkylene glycol moiety.

ABEX UPTX: 20040205

ADMINISTRATION - The dosage of (a) is 0.05 - 5 mg/kg body weight. The administration is oral (claimed).

EXAMPLE - No relevant example given.

L115 ANSWER 3 OF 21 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2003-402880 [38] WPIX

DNC C2003-107140

TI Synthesizing insulin polypeptide-**oligomer conjugate**, by coupling proinsulin polypeptide with **oligomer** having **hydrophilic** and **lipophilic** moiety, and cleaving peptides from proinsulin polypeptide-**oligomer conjugate**.

DC A25 A96 B04 D16

IN EKWURIBE, N N; RADHAKRISHNAN, B; SOLTERO, R; PUSKAS, M; SANGAL, D

PA (EKWU-I) EKWURIBE N N; (RADH-I) RADHAKRISHNAN B; (SOLT-I) SOLTERO R; (PUSK-I) PUSKAS M; (SANG-I) SANGAL D; (NOBE-N) NOBEX CORP

CYC 102

PI WO 2003022996 A2 20030320 (200338)* EN 113 C12N000-00

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

US 2003087808 A1 20030508 (200338) A61K038-28 <--
US 2003228652 A1 20031211 (200382) C12P021-06
US 2003229009 A1 20031211 (200382) A61K038-28 <--
EP 1430082 A2 20040623 (200441) EN C07K014-62 <--
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR

ADT WO 2003022996 A2 WO 2002-US28428 20020906; US 2003087808 A1 Provisional US 2001-318197P 20010907, US 2001-36744 20011221; US 2003228652 A1 Provisional US 2001-318197P 20010907, CIP of US 2001-36744 20011221, CIP of US 2003-382022 20030305, US 2003-389499 20030317; US 2003229009 A1 Provisional US 2001-318197P 20010907, CIP of US 2001-36744 20011221, US 2003-382022 20030305; EP 1430082 A2 EP 2002-766246 20020906, WO 2002-US28428 20020906

FDT EP 1430082 A2 Based on WO 2003022996

PRAI US 2002-349462P 20020118; US 2001-318197P 20010907;
US 2001-36744 20011221; US 2003-382022 20030305;
US 2003-389499 20030317

IC ICM **A61K038-28**; **C07K014-62**; C12N000-00; C12P021-06
ICS **C07K014-62**

AB WO2003022996 A UPAB: 20040112
NOVELTY - Synthesizing insulin polypeptide-**oligomer conjugate** (I), comprising contacting proinsulin polypeptide with an **oligomer** having **hydrophilic** and **lipophilic** moiety under conditions sufficient to couple **oligomer** to insulin polypeptide portion of proinsulin polypeptide and provide proinsulin polypeptide-**oligomer conjugate** (II), and cleaving peptides from (II) to provide (I), is new.

DETAILED DESCRIPTION - Synthesizing (M) an insulin polypeptide-**oligomer conjugate**, comprising:

(a) contacting a proinsulin polypeptide having an insulin polypeptide coupled to one or more peptides by peptide bond(s) capable of being cleaved to yield the insulin polypeptide with an **oligomer** comprising a **hydrophilic** moiety and a **lipophilic** moiety under conditions sufficient to couple the **oligomer** to the insulin polypeptide portion of the proinsulin polypeptide and provide a proinsulin polypeptide-**oligomer conjugate**; and

(b) cleaving the one or more peptides from the proinsulin polypeptide-**oligomer conjugate** to provide the insulin polypeptide-**oligomer conjugate**.

INDEPENDENT CLAIMS are also included for:

(1) a proinsulin polypeptide-**oligomer conjugate** comprising a proinsulin polypeptide comprising an insulin polypeptide, and an **oligomer** comprising a **hydrophilic** moiety and a **lipophilic** moiety coupled to the insulin polypeptide portion of the proinsulin polypeptide;

(2) a composition of insulin-**oligomer conjugates** consisting essentially of insulin-**oligomer monoconjugates** comprising insulin coupled at an amino function of the lysine B29 position to an **oligomeric** moiety having the structure (S1);

(3) synthesizing (M1) a C-peptide polypeptide-**oligomer conjugate**, by contacting a pro-C-peptide polypeptide comprising a C-peptide polypeptide coupled to one or more peptides by peptide bond(s) that are cleavable to yield the C-peptide polypeptide with an **oligomer** under conditions sufficient to couple the **oligomer** to the C-peptide polypeptide portion of the pro-C-peptide polypeptide and provide a pro-C-peptide polypeptide-**oligomer conjugate**, and cleaving the one or more peptides from the pro-C-peptide polypeptide-**oligomer conjugate** to provide the C-peptide polypeptide-**oligomer conjugate**; and

(4) a C-peptide polypeptide-**oligomer conjugate** provided by (M1).

(S1) is -C(O)-(CH2)n(OC2H4)mOR.
n = 1-30;
m = 1-50; and
R = alkyl.
ACTIVITY - Antidiabetic.
No biological data is given.
MECHANISM OF ACTION - None given.
USE - (M) is useful for synthesizing an insulin polypeptide-**oligomer conjugate** (claimed) for treating diseases including diabetes.
ADVANTAGE - (M) is rapid, and provides a commercially less expensive and/or higher yielding manufacturing scheme for producing insulin-**oligomer conjugates** where site-specific **conjugation** is desirable.
Dwg.0/16
FS CPI
FA AB; DCN
MC CPI: A10-E01; A12-V01; A12-W11L; B01-D02; B04-C03C; B04-J03A; B09-D01; B10-A11A; B10-A11B; B10-A12A; B10-A12B; B10-A12C; B10-B02B; B10-B03B; B10-C01; B10-C04; B14-S04; D05-A02; D05-A02C; D05-H10
TECH UPTX: 20040112
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: The method involves contacting the proinsulin polypeptide with the **oligomer**, by contacting the **oligomer** with an activating agent under conditions sufficient to provide an activated **oligomer** capable of coupling to a nucleophilic functionality on the proinsulin polypeptide, and contacting the activated **oligomer** with the proinsulin polypeptide under conditions sufficient to provide the proinsulin polypeptide-**oligomer conjugate.** The contacting the **oligomer** with the activating agent and contacting the activated **oligomer** with the proinsulin polypeptide is performed in situ. The molar ratio of activated **oligomer** to proinsulin polypeptide is greater than 4:1. The insulin polypeptide has an A-chain polypeptide and a B-chain polypeptide, and where one or more peptides comprise a connecting peptide coupled at a first end to the C-terminus of the B-chain polypeptide and coupled at a second end to the N-terminus of the A-chain polypeptide. The connecting peptide is a C-peptide polypeptide, or C-peptide. The proinsulin polypeptide is proinsulin. The connecting peptide is devoid of lysine residues. The connecting peptide has a terminal amino acid residue at the first end, and where the cleaving of the connecting peptide from the proinsulin polypeptide-**oligomer conjugate**, involves contacting the proinsulin polypeptide-**oligomer conjugate** with a first enzyme under conditions sufficient to provide a terminal amino acid residue-insulin polypeptide-**oligomer conjugate**, and contacting the terminal amino acid residue-insulin polypeptide-**oligomer conjugate** with a second enzyme under conditions sufficient to provide the insulin polypeptide-**oligomer conjugate.** The terminal amino acid residue is an arginine residue. The insulin polypeptide is insulin, and where the connecting peptide is human C-peptide. The contacting of the proinsulin polypeptide-**oligomer conjugate** with a first enzyme and contacting of the terminal amino acid residue-insulin polypeptide-**oligomer conjugate** with a second enzyme occur substantially concurrently. The first enzyme and the second enzyme are provided in a mixture comprising the first enzyme and the second enzyme. The first enzyme is trypsin, and the second enzyme is carboxy peptidase B. The peptides further comprise a leader peptide coupled to the N-terminus of the B-chain polypeptide. The leader peptide is devoid of lysine residues. Cleaving of one or more peptides from the proinsulin polypeptide-**oligomer conjugate**, comprises contacting the proinsulin polypeptide-**oligomer conjugate** with one or more enzymes that are capable of cleaving the bond(s) between the peptides and the insulin polypeptide under conditions sufficient to cleave

the peptides from the proinsulin polypeptide-**oligomer conjugate**. The enzymes are selected from trypsin, carboxy peptidase B, and their mixtures. The **oligomer** comprises the structure of formula (I).
A-Lj-Gk-R-G'm-R'-Gn-T (I).
A = activatable moiety selected from -C(O)-OH, C(S)-OH, -C(S)-SH, -OH, -SH, and NH2;
L = linker moiety selected from alkyl moieties and fatty acid moieties;
G' and G = spacer moieties and are individually selected from sugar moieties, cholesterol, and glycerine moieties;
R and R' = **lipophilic** moiety and polyalkylene glycol moiety; and
T = terminating moiety selected from alkyl moiety, sugar moiety, cholesterol, adamantane, alcohol moiety, and fatty acid moiety; and
j, k, m, and n = 0 or 1.
The **oligomer** comprises the structure of formula (II).
A-X(CH2)mY(C2H4O)nR (II).
A = -C(O)-OH, C(S)-OH, -C(S)-SH, -OH, -SH, or NH2;
X = oxygen atom or a covalent bond, with the proviso that X is not an oxygen atom when A is -OH;
Y = ester, ether, carbamate, carbonate, or amide bonding moiety;
m = 1-30;
n = 1-50; and
R = alkyl moiety, sugar moiety, cholesterol, adamantane, alcohol moiety, or fatty acid moiety.
The **oligomer** comprises the structure of formula (III)
A-(CH2)m(OC2H4)mOR (III).
A = -C(O)-OH, C(S)-OH, -C(S)-SH, -OH, -SH, or NH2;
m and n = 1-25; and
R = alkyl.
The **oligomer** comprises the structure of formula (IV).
HO-C(O)-(CH2)n(OC2H4)mOR (IV).
n = 1-30;
m = 1-50; and
R = alkyl.
The **oligomer** comprises the structure of formula (V).
HO-C(O)-(CH2)5(OC2H4)7OCH3 (V).
The **oligomer** is coupled to the lysine at the B29 position of the insulin. The insulin polypeptide-**oligomer conjugate** is **amphiphilically** balanced. The **oligomer** is present as a substantially monodispersed mixture. The yield of insulin polypeptide-**oligomer conjugate** is greater than 75 percent. The pro-C-peptide polypeptide is a proinsulin polypeptide. The pro-C-peptide polypeptide is proinsulin. The peptide is an insulin polypeptide, preferably insulin. The **oligomer** comprises a **hydrophilic** moiety and a **lipophilic** moiety. Cleaving the peptide from the pro-C-peptide polypeptide-**oligomer conjugate**, by contacting the pro-C-peptide polypeptide-**oligomer conjugate** with enzymes that are capable of cleaving the bond(s) between the peptide and the C-peptide polypeptide under conditions sufficient to cleave peptides from the pro-C-peptide polypeptide-**oligomer conjugate**.
Preferred **Conjugate**: The proinsulin polypeptide comprises an insulin polypeptide having an A-chain polypeptide and B-chain polypeptide, a connecting peptide coupled at a first end to the C-terminus of the B-chain polypeptide and coupled at a second end to the N-terminus of the A-chain polypeptide, and a leader peptide coupled to the N-terminus of the B-chain polypeptide. The **oligomer** is coupled to the insulin polypeptide portion of the proinsulin polypeptide at a lysine residue of the insulin polypeptide. The insulin polypeptide is insulin and the lysine residue is at B29 position of the insulin.
Preferred Composition: The **oligomeric** moiety has the structure -C(O)-(CH2)5(OC2H4)7OCH3.

EXAMPLE - 2.23x10 to the power -3 mmol portion of proinsulin I (recombinant proinsulin I (molecular weight = 10642 Daltons)) was dissolved in 10 ml of dimethylsulfoxide (DMSO). To the solution was added 324 micro-l of triethylamine. The resulting solution was allowed to stir for 5 minutes, and then a solution of activated methylheptaethylene glycol(PEG7)-hexyl **oligomer** (4-6 mol eq., sufficient to covert all proinsulin I to the **triconjugate**) in acetonitrile was added. The course of the **conjugation** (acylation) reaction was monitored by high performance liquid chromatography (HPLC). When reaction appears to be complete (i.e., no **unconjugated** proinsulin I was observed by HPLC), it was quenched by addition of 3.54 ml of 5 % aqueous trifluoroacetic acid solution. The reaction mixture was then processed and exchanged into 100 mm Tris-HCl Buffer, pH 7.6. The HPLC profile of the product mixture, **oligomer-conjugated** recombinant proinsulin I, was expected to show peaks corresponding to **triconjugate** and **diconjugate** only. An aliquot of the Tris-HCl solution **oligomer-conjugated** recombinant proinsulin I product mixture was analyzed by HPLC to determine the polypeptide concentration. A solution of tyrpsin was prepared in 100 mM Tris-HCl buffer, pH 7.6. A solution of carboxypeptidase B was prepared in 100 mM Tris-HCl buffer, pH 7.6. The product mixture (0.424 micro-mol/ml) was then allowed to react with trypsin (5.97x10 to the power -4 micro-mol/ml) and carboxypeptidase B (1.93x10 to the power -4 micro-mol/ml). After 30 minutes, the reaction was quenched by the addition of 1.58 ml of 1 % trifluoroacetic acid in acetonitrile. The major products were identified by HPLC retention time (relative to the retention times of known reference standards) and mass spectral analysis. Lys(B29)-Hexyl-PEG7-**oligomer-conjugated** insulin, the only insulin **conjugate** that was present, was expected to be obtained in near 95 % yield. Lys1-Hexyl-PEG7-**oligomer-conjugated** C-peptide was also obtained in near quantitative yield.

L115 ANSWER 4 OF 21 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-371726 [35] WPIX
CR 2003-354500 [33]
DNC C2003-098581
TI Composition useful for the treatment of e.g. diabetes comprises insulin-drug **conjugate**, fatty acid component and bile salt component.
DC A25 A96 B04 B05
IN BOVET, L L; EKWURIBE, N N; HICKEY, A; RADHAKRISHNAN, B; REHLANDER, B; SOLTERO, R; REHLAENDER, B
PA (BOVE-I) BOVET L L; (EKWU-I) EKWURIBE N N; (HICK-I) HICKEY A; (RADH-I) RADHAKRISHNAN B; (REHL-I) REHLANDER B; (SOLT-I) SOLTERO R; (REHL-I) REHLAENDER B; (NOBE-N) NOBEX CORP
CYC 101
PI WO 2003022208 A2 20030320 (200335)* EN 65 A61K000-00
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
US 2003083232 A1 20030501 (200336) A61K038-28 <--
US 2004038866 A1 20040226 (200416) A61K038-28 <--
ADT WO 2003022208 A2 WO 2002-US28429 20020906; US 2003083232 A1 Provisional US 2001-318193P 20010907, Provisional US 2002-377865P 20020503, US 2002-235381 20020905; US 2004038866 A1 Provisional US 2001-318193P 20010907, Provisional US 2002-377865P 20020503, CIP of US 2002-235281 20020905, CIP of US 2002-235284 20020905, US 2003-382155 20030305
PRAI US 2002-377865P 20020503; US 2001-318193P 20010907;
US 2002-235381 20020905; US 2002-235281 20020905;

US 2002-235284 20020905; US 2003-382155 20030305
IC ICM A61K000-00; **A61K038-28**
ICS A61K031-56; A61K031-57
AB WO2003022208 A UPAB: 20040305
NOVELTY - A composition (C1) comprises (weight/volume %):
(a) a fatty acid component (0.1 - 15),
(b) a bile salt component (0.1 - 15); and
(c) an insulin drug-**oligomer conjugate** having an insulin drug covalently coupled to an **oligomeric** group.
(a) and (b) are in a weight-to-weight ratio of 1:5 - 5:1 (preferably 1:2 - 2:1).
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for providing (C1) involving either selecting an amount of (b) based on the ability of (b) to increase the solubility of (a) when (C1) has a pH of at most 8.5; or selecting an amount of (a) based on the ability of (a) to alter the precipitation of (b) (preferably lower the precipitation point of (b) in (C1) at pH of at most 5.5).
ACTIVITY - Antidiabetic.
MECHANISM OF ACTION - Insulin level enhancer.
A liquid oral composition (T1) comprising (weight/volume%) human insulin-**oligomer conjugate** (HIM2) (0.6), sodium cholate (3), oleic acid NF (1), 0.25 % sucralose (0.8), strawberry flavor (0.4), capric acid (0.5), lauric acid (0.5), citric acid (6.72), trolamine NF (5.22), tromethamine (4.24) and sodium hydroxide NF (1.88), was administered in an amount of 0.25 mg/ml to healthy human volunteers. The volunteers without administration of (T1) were maintained as control. The blood analysis for the plasma levels of glucose and insulin showed that the insulin levels (micro U/ml) in the plasma were: 104/10 and 65/20 pre-prandially and post-prandially after 15 minutes of administration of (T1) for test/control respectively; the plasma glucose levels (mg/ml) were 83/62 and 60/92 pre-prandially and post-prandially after 15 minutes administration of (T1) for test/control respectively.
USE - For treating insulin deficiency (claimed) diseases e.g. diabetes.
ADVANTAGE - (C1) improves bioavailability and glucose lowering activity of the insulin. (a) lowers the precipitation point of (b) compared to that if (a) was not present in (C1). (b) lowers the solubility point of (a) compared to that if (b) was not present in (C1). (a) facilitates the precipitation of (b) as first bile particles and re-solubilization upon return to a pH above the precipitation point of (b), more quickly than second bile salt particles precipitating in absence of (a). (b) facilitates solubilization of (a) at pH 8.2 and (a) facilitates solubilization of (b) at a pH 5.5. (C1) provides synergistic effect of (a), (b) and (c) and can be administered through non-injectable routes.
Dwg.1/9
FS CPI
FA AB; GI; DCN
MC CPI: A10-E01; A12-V01; B01-D02; B04-B01B; B04-B04H; B04-J02; B04-J03A; B04-N04; B05-A01B; B05-C07; B07-A02; B10-B03B; B10-C02; B10-C04E; B14-S04
TECH UPTX: 20030603
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The pH of (C1) is 6.2 - 9. (C1) additionally comprises a buffering component. Preferred Components: The insulin drug is an insulin polypeptide (preferably human insulin). The **oligomeric** moiety is coupled to the lysine at the B29 position of the human insulin.

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: (b) comprises a salt of cholic acid. (a) comprises a medium and long-chain fatty acid components. The buffering component comprises tris-base and trolamine. The **oligomeric** group comprises **hydrophilic** and **lipophilic** groups. (c) is present as a monodispersed mixture. (c)

is the **conjugate** of formula D1-B'-Lj-Gk-R-G'm-R'-G2n-T (I), D1-X(CH2)m'Y(C2H4O)n'R1 (II), D1-X(CH2)m'(OC2H4)n'OR1 (III) or D1-NH-C(=O)(CH2)m'(OC2H4)n'OR1 (IV).
B' = bonding group;
L = linker group;
G, G' and G2 = spacer groups;
D1 = insulin drug;
R, R' = **lipophilic** or polyalkylene glycol group;
T = terminating group;
j, k, m and n = 0 or 1;
X, Y = (thio)ester, ether, (thio)carbamate, (thio)carbonate, amide, urea or covalent bond;
m' = 1 - 24 (preferably 5);
n' = 1 - 50 (preferably 7); and
R1 = alkyl, sugar, cholesterol, adamantane, alcohol or fatty acid (preferably CH3).

TECHNOLOGY FOCUS - BIOLOGY - Preferred Components: The insulin polypeptide is an insulin analog selected from Gly-A21 insulin, Gly-A21Gln-B3 insulin, Ala-A21 insulin, Ala-A21Gln-B3 insulin, Gln-B3 insulin, Gln-B30 insulin, Gly-A21-Glu-B30 insulin, Gly-A21 Gln-B3 Glu-B30 insulin, Gln-B3-Glu-B30 insulin, Asp-B28 insulin,
Lys-B28 insulin, Leu-B28 insulin, Val-B28 insulin, Ala-B28 insulin,
Asp-B28 Pro-B29 insulin, Lys-B28 Pro-B29 insulin, Leu-B28 Pro-B29 insulin,
Val-B28 Pro-B29 insulin or Ala-B28 Pro-B29 insulin.

ABEX UPTX: 20030603

SPECIFIC COMPOUNDS - Sodium cholate is specifically claimed as (b).

ADMINISTRATION - (C1) in the form of solid dosage is administered orally and in the form of liquid dosage is administered orally or parenterally (claimed) (including subcutaneously, intramuscularly, intradermally, intraarticularly, intraperitoneally, intracerebrally, intraarterially or intravenously), or rectally, topically, buccally, vaginally, transdermally or by inhalation via aerosol. The dosage of (C1) is 0.1 - 50 mg/kg. The dosages (mg/kg) for intravenous, oral and intramuscular administration are 10, 10 - 50 and 0.5 - 5 respectively.

EXAMPLE - An oral liquid composition comprised (w/v %): human insulin-**oligomer conjugate** (HIM2) (0.6), sodium cholate (3), oleic acid NF (1), 25 % sucralose (0.8), strawberry flavor (0.4), capric acid (0.5), lauric acid (0.5), citric acid (6.72), trolamine NF (5.22), tromethamine (4.24), sodium hydroxide NF (1.88), 5N sodium hydroxide (balance), 5N hydrochloric acid (balance) and sterile water (balance).

L115 ANSWER 5 OF 21 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-354500 [33] WPIX
CR 2003-371726 [35]
DNC C2003-093403
TI Composition used for treating bone disorders e.g. osteoporosis comprises drug **oligomer conjugate**, fatty acid component and bile salt component.
DC A25 A96 B04 B05
IN EKWURIBE, N N; HICKEY, A; LI LI, B; OPAWALE, F; REHLANDER, B; SOLTERO, R; BOVET, L L; REHLAENDER, B; BEATON, R J; CLOWATER, G A; HETHERINGTON, R G; PALMER, S J A M; RADZIKOWSKA, M; STUART, A M L
PA (EKWU-I) EKWURIBE N N; (HICK-I) HICKEY A; (LIBB-I) LI LI B; (OPAW-I) OPAWALE F; (REHL-I) REHLANDER B; (SOLT-I) SOLTERO R; (BOVE-I) BOVET L L; (REHL-I) REHLAENDER B; (IMAG-N) IMAGICTV INC; (NOBE-N) NOBEX CORP
CYC 101
PI WO 2003022210 A2 20030320 (200333)* EN 48 A61K000-00
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK

DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA
ZM ZW

US 2003069170 A1 20030410 (200333) A61K038-23 <--
US 2004017387 A1 20040129 (200413) G09G005-00
US 2004046780 A1 20040311 (200419)# G09G005-00

ADT WO 2003022210 A2 WO 2002-US28536 20020906; US 2003069170 A1 Provisional US 2001-318193P 20010907, Provisional US 2002-377865P 20020503, US 2002-235284 20020905; US 2004017387 A1 Provisional US 2001-318193P 20010907, Provisional US 2002-377865P 20020503, CIP of US 2002-235281 20020905, CIP of US 2002-235284 20020905, US 2003-382069 20030305; US 2004046780 A1 US 2002-235281 20020905

PRAI US 2002-377865P 20020503; US 2001-318193P 20010907;
US 2002-235284 20020905; US 2002-235281 20020905;
US 2003-382069 20030305

IC ICM A61K000-00; **A61K038-23**; G09G005-00
ICS A61K031-202; A61K031-56; **A61K038-00**

AB WO2003022210 A UPAB: 20040318
NOVELTY - Composition (C1) comprises (in weight/volume %): a fatty acid component (a) (0.1-15), a bile salt component (b) (0.1-15) and an drug-**oligomer conjugate** having a drug covalently coupled to an **oligomeric** group. (a) And (b) are contained in a weight-to-weight ratio of 1:5-5:1 (preferably 1:2-2:1).

ACTIVITY - Osteopathic; Cytostatic.

MECHANISM OF ACTION - None given.

USE - Used for treating bone disorders (claimed) e.g. osteoporosis, Paget's disease and hypercalcemia.

ADVANTAGE - (a) Reduces the precipitation point of (b) compared to that if (a) is not present in (C1). (b) Reduces the solubility point of (a) compared to that if (b) is not present in (C1). (a) Facilitates the precipitation of (b) as first bile particles and re-solubilization upon return to a pH above the precipitation point of (b), more rapidly than second bile salt particles precipitating in the absence of (a). (b) Facilitates solubilization of (a) at pH 8.2 and (a) facilitates solubilization of (b) at a pH 5.5. The composition provides synergistic effect in the administration of drug-**oligomer conjugates**

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Dwg.0/13

FS CPI
FA AB; DCN
MC CPI: A12-V01; B01-D02; B10-A07; B10-B01B; B10-C04E; B14-N01
TECH UPTX: 20030526

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The pH of (C1) is 6.2-9. (C1) Additionally comprises a buffering component.

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: The buffering agent comprises tris-base or trolamine. (b) Comprises a cholic acid, preferably sodium cholate. (a) Comprises a medium- and long- chain fatty acid component. The **oligomer** groups comprise CH3O(C2H4O)7-(CH2)7-C(O). The drug-**oligomer conjugate** is a monodispersed mixture. The **oligomeric** group comprises a **hydrophilic** or a **lipophilic** group.

The drug **oligomer conjugate** is of formula Drug-B'-Lj-Gk-R-G1m-R'-G2n-T (I), Drug-X(CH2)m'Y(C2H4O)n'R1 (II), Drug-X(CH2)m'(OC2H4)n'OR1 (III) or Drug-NH-C(=O)-(CH2)m'(OC2H4)n'OR1 (IV).

B' = a bonding group;
L = a linker group;
G, G1, G2 = spacer groups;
R, R' = **lipophilic** group or polyalkylene glycol group;
T = terminating group;
j, k, m, n = 0 or 1;
X, Y = ester, thioester, ether, carbamate, thiocarbamate, carbonate, thiocarbonate, amide, urea or covalent bond;

m' = 1-24);
n' = 1-50, and
R1 = alkyl, sugar, cholesterol, adamantane, alcohol or fatty acid, provided that R and R' are not both **lipophilic** or polyalkylene glycol groups.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Compounds: The drug comprises a calcitonin polypeptide (preferably salmon calcitonin). The drug **oligomer** group comprises salmon calcitonin coupled to two **oligomeric** groups, in which one **oligomer** group is coupled to the lysine at the 11 position of the calcitonin and the other **oligomeric** group coupled to the lysine 18 position of the salmon calcitonin.

ABEX UPTX: 20030526

ADMINISTRATION - The dosage is 10-50 mg/kg orally in solid or liquid dosage form or 0.5-5 mg/kg intramuscularly. (C1) is administered orally in solid or liquid dosage form (claimed). (C1) is also administered rectally, topically, inhalation (e.g. via an aerosol), buccally (e.g. sublingually), vaginally, parenterally (e.g. subcutaneously, intramuscularly, intradermally, intraarticularly, intrapleurally, intraperitoneally, intracerebrally, intraarterially or intravenously), topically or transdermally.

EXAMPLE - A tablet formulation comprised (in g): Lyo portion (127.6) (human insulin-**oligomer conjugate** (HIM2) (2.50), sodium cholate (30), oleic acid, NF (10), 25% sucralose (8), strawberry flavor (4), capric acid (5), lauric acid (5), anhydrous citric acid (67.2), trolamine, NF (52.2), tromethamine (42.4), sodium hydroxide NF (18.8), 5N sodium hydroxide (balance), 5N hydrochloric acid (balance) and sterile water for irrigation (balance), citric acid (29.7), sodium citrate dihydrate (84.2), tris base (tris(hydroxymethyl)aminomethane) (106.7), microcrystalline cellulose (24.8) and explotab (9.4).

L115 ANSWER 6 OF 21 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-221302 [21] WPIX
DNC C2003-056080
TI Monodispersed mixture of **conjugates** useful in treatment of disease e.g. diabetes comprises drug coupled to **oligomer** containing polyalkylene glycol moiety.
DC A96 B04 D16
IN ANSARI, A M; EKWURIBE, N N; ODENBAUGH, A L; PRICE, C H
PA (NOBE-N) NOBEX CORP; (ANSA-I) ANSARI A M; (EKWU-I) EKWURIBE N N; (ODEN-I) ODENBAUGH A L; (PRIC-I) PRICE C H
CYC 101
PI WO 2002098446 A1 20021212 (200321)* EN 101 A61K038-02 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
BR 2001006401 A 20030211 (200321) A61K047-48
JP 2003104913 A 20030409 (200333) 308 A61K047-48
US 2003228275 A1 20031211 (200382) A61K038-00 <--
EP 1404355 A1 20040407 (200425) EN A61K038-02 <--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
ADT WO 2002098446 A1 WO 2002-US17567 20020604; BR 2001006401 A BR 2001-6401 20011011; JP 2003104913 A JP 2001-317307 20011015; US 2003228275 A1 US 2001-873797 20010604; EP 1404355 A1 EP 2002-737357 20020604, WO 2002-US17567 20020604
FDT EP 1404355 A1 Based on WO 2002098446

PRAI US 2001-873797 20010604
IC ICM **A61K038-00**; **A61K038-02**; A61K047-48
ICS A61K031-765; **A61K038-17**; **A61K038-18**; **A61K038-19**; **A61K038-22**; **A61K038-23**; **A61K038-28**; A61K039-02; A61K039-12; A61K039-385; A61K047-34; A61P005-00; A61P043-00; **C07K001-107**; **C07K001-113**; **C07K002-00**; **C07K014-475**; **C07K014-52**; **C07K014-575**; **C07K014-585**
AB WO 200298446 A UPAB: 20030328
NOVELTY - A substantially monodispersed mixture of **conjugates** comprises a drug coupled to an **oligomer** (a) containing a polyalkylene glycol moiety (b).

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for synthesizing a monodispersed mixture of **conjugate**, that involves:

(i) reacting a monodispersed mixture containing compounds of formula R1(OC2H4)m-O-X+ (I) with a substantially monodispersed mixture containing compounds of formula R2(OC2H4)q-OMs (II) to form a monodispersed mixture comprising polymers of formula R2(OC2H4)m+q-OR1 (III);

(ii) activating (III) to form a monodispersed mixture of activated polymers capable of reacting with a drug; and

(iii) reacting the monodispersed mixture of activated polymers with a monodispersed mixture of drugs to form a monodispersed mixture of **conjugates** comprising drug coupled to an **oligomer** containing polyethylene glycol with m+p subunits.

R1 and R2 = H or lipophilic moiety;
m, q = 1 - 25; and
X+ = positive ion.
ACTIVITY - Antidiabetic.
MECHANISM OF ACTION - None given.
USE - In the treatment of disease states e.g. insulin deficiency.

Male CF-1 mice were housed in a room. Mice were acclimated to housing conditions for 48 - 72 hours prior to the day of experiment. Prior to dosing, mice were fasted overnight and water was provided ad libitum. Mice were distributed into groups of five animals per time point and were administered a single oral dose of a PEG7-octyl-(sCT), **diconjugate** (Octyl Di) (test) or salmon calcitonin (sCT or Calcitonin) for comparison purposes. Oral doses were administered at 10 ml/kg in a phosphate-buffered PEG7-octyl-sCT, **diconjugate** formulation. The buffered formulation was prepared by adding phosphate buffer (80 mL) in a beaker. The sodium cholate was added to the phosphate buffer with stirring until dissolved. The deoxy cholate was then added and stirring was continued until dissolved. The PEG7-octyl-sCT, **diconjugate**, solution was added. The remaining phosphate buffer was added to achieve a final weight of 100 g. Dose-response curves were constructed. At appropriate time points, mice were ether-anesthetized, the vena cavae exteriorized, and blood samples were obtained. Blood aliquots were clotted at 22 deg. C for 1 hour, and the sera removed and pipetted into a clean receptacle. Total serum calcium was determined for each animal. Serum calcium data were plotted and pharmacokinetic parameters determined. Means and standard deviations (or standard errors) were calculated and plotted to determine effect differences among dosing groups. The % baseline calcium drop at 2 micro g/kg dose for the test was 21%. The in vitro activity of PEG7-octyl-sCT and PEG7-decyl-sCT mono- and **diconjugates**, the stearate-PEG6-sCT, **diconjugate**, and stearate-PEG8-sCT, **diconjugate**, appeared to have in vivo activity that was comparable with the in vivo activity observed for the PEG7-octyl-sCT and PEG7-decyl-sCT, mono- and di-**conjugates.** The improved in vivo activity of the stearate containing **conjugates** indicated that these **conjugates** were undergoing hydrolysis in vivo to provide an active salmon calcitonin or active salmon calcitonin-PEG **conjugate.**

ADVANTAGE - The mixture exhibits greater in vivo/in vitro activity

than the in vivo/in vitro activity of the polydispersed mixture of drug-**oligomer conjugates** having same number of average molecular weight as the mixture. The mixture has increased resistance to degradation by chymotrypsin when compared to the resistance to degradation by chymotrypsin of a polydispersed mixture of insulin drug-**oligomer conjugate** mixture having same number average molecular weight as the mixture. The mixture has inter-subject variability that is less than the inter-subject variability of a polydispersed mixture of insulin drug-**oligomer conjugates** having same number average molecular weight as the mixture.

Dwg.0/43

FS CPI

FA AB; GI; DCN

MC CPI: A12-V01; B04-C01; B04-C03; B04-C03C; B04-H01; B04-J01; B04-N01; B04-N02; B04-N03; B14-S04; D05-H12D

TECH UPTX: 20030328

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred **Conjugates**: The mixture has a dispersity coefficient (DC) greater than 10000 (preferably greater than 100000, especially greater than 500000) daltons as given in formula (X) or has molecular weight distribution with a standard deviation of less than 22 (preferably less than 14, especially less than 11) daltons. In each **conjugate**, the **oligomer** has the optionally same number of polyalkylene glycol subunit. When each **conjugate** has same molecular weight, the **conjugate** has formula Drug-(B'-Lh-Gi-Ra-G'j-R'b-Qk-T)p-. The **conjugate** is **amphiphilically** balanced such that it is aqueously soluble and able to penetrate biological membranes. At least 96, 97, 98 or 99% of the **conjugate** in the mixture has the same molecular weight. Each **conjugate** comprises several **oligomers.**

n = number of different molecules in the sample;
Ni = number of ith molecules in the sample;
Mi = mass of the ith molecule;
B' = bonding moiety;
L = linking moiety;
G, G' and Q = spacer moiety;
R' = lipophilic moiety or polyalkylene glycol (preferably polyethylene glycol having 7 polyethylene glycol subunits);
R = lipophilic moiety or polyalkylene glycol;
T = terminating moiety;
i, j, k = 0 or 1 (preferably 0);
a and b = 0 or 1 (preferably 1);
h = 0 or 1;
p = 1 - number of nucleophilic residues on the drug; and
provided that:
(a) when R is the polyalkylene glycol moiety then a is 1; and
(b) when R' is the polyalkylene glycol moiety then b is 1.
Preferred Method: The method further involves:
(i) reacting a monodispersed mixture comprising compounds of formula R2(OC2H4)q-OH (V) with a methanesulfonyl chloride to form a monodispersed mixture comprising (II);
(ii) reacting a monodispersed mixture comprising compounds of formula R2-OMs (VI) with a monodispersed mixture comprising compounds of formula R3(OC2H4)m-O- X+2 (VII) to form a monodispersed mixture comprising compounds of formula R3(OC2H4)m-OR2 (VIII);
(iii) reacting (VIII) to form a mixture comprising (V);
(iv) reacting a monodispersed mixture comprising a compound of formula R1(OC2H4)q-OH (IV) to form the substantially monodispersed mixture comprising (I).
R3 = benzyl, trityl or THP;
X+2 = positive ion.
The activating of the mixture involves reaction of (III) with N-hydroxy succinimide to form an activated polymer capable of reacting with a drug. The reaction of mixture of activated polymers with a monodispersed mixture

of polypeptides involves reacting the mixture with at least one functionality of the polypeptide to form monodispersed mixture of **conjugates** comprising the polypeptide coupled to an **oligomer** containing polyethylene glycol with m+q subunits.

TECHNOLOGY FOCUS - POLYMERS - Preferred **Oligomer**: (a) is devoid of lipophilic moiety. (a) is covalently coupled to the drug or a nucleophilic residue of the polypeptides. (a) further comprises a lipophilic moiety optionally covalently coupled to the second polyethylene glycol. Each **oligomer** of the several **oligomers** is same. (a) comprise a first polyalkylene glycol moiety covalently coupled to the drug by a non-hydrolyzable bond and a second polyalkylene glycol covalently coupled to the first polyalkylene glycol moiety by a hydrolyzable bond. The drug in synthesis method is a polypeptide. Preferred Components: (b) has at least 2, 3 or 4 (preferably at least 5 or 6, especially at least 7) polyalkylene glycol subunits. (b) is lower alkyl polyalkylene glycol (preferably polyethylene glycol or uniform polypropylene glycol).
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Drug: The drug is a polypeptide. The polypeptide is adrenocorticotropic hormone peptide, adrenomedullin peptide, allatostatin peptide, amylin peptide, amyloid beta-protein fragment peptide, angiotensin peptide, antibiotic peptide, antigenic polypeptide, anti-microbial peptide, apoptosis related peptide, atrial natriuretic peptide, bag cell peptide, bombesin peptide, bone GLA peptide, bradykinin peptide, brain natriuretic peptide, C-peptide, C-type natriuretic peptide, calcitonin peptide, calcitonin gene related peptide, CART peptide, casomorphin peptide, chemotactic peptide, cholecystokinin peptide, colony-stimulating factor peptide, corticortropin releasing factor peptide, cortistatin peptide, cytokine peptide, dermorphin peptides, dynorphin peptide, endorphin peptide, endothelin peptide, ETa receptor antagonist peptide, ETb receptor antagonist peptide, enkephalin peptide, fibronectin peptide, galanin peptide, gastrin peptide, glucagon peptide, Gn-RH associated peptide, growth factor peptide, growth hormone peptide, GTP-binding protein fragment peptide, guanylin peptide, inhibin peptide, insulin peptide, interleukin peptide, laminin peptide, leptin peptide, leucokinin peptide, luteinizing hormone-releasing hormone peptide, mastoparan peptide, mast cell degranulating peptide, melanocyte stimulating hormone peptide, morphiceptin peptide, motilin peptides neuro-peptide, neuropeptide Y peptide, neurotropic factor peptide, orexin peptide, opioid peptide, oxytocin peptide, PACAP peptide, pancreastatin peptide, pancreatic polypeptide, parathyroid hormone peptide, parathyroid hormone-related peptide, peptide T peptide, prolactin-releasing peptide, peptide YY peptide, renin substrate peptide, secretin peptide, somatostatin peptide, substance P peptide, tachykinin peptide, thyrotropin-releasing hormone peptide, toxin peptide, vasoactive intestinal peptide, vasopressin peptide, or virus related peptide.

ABEX UPTX: 20030328

ADMINISTRATION - The composition is administered in a dosage of 10 mg - 100 g orally, rectally, topically, by inhalation (by aerosol), buccally (such as sublingually), vaginally, parenterally (including subcutaneously, intramuscularly, intradermally, intraarticularly, intrapleurally, intraperitoneally, intracerebrally, intraarterially or intravenously), transdermally or topically. For oral administration the dosage is 10 - 50 and for intramuscular injection the dosage is 0.5 - 5 mg/kg.

EXAMPLE - A mixtures of polypeptide was dissolved in anhydrous N,N'-dimethylformamide (DMF). Then TEA and a mixture of an activated **oligomer** of 6(2-(2-(2-(2-(2-(2-methoxyethoxy)ethoxy)-ethoxy)ethoxy)-ethoxy)-ethoxy)-ethoxy)-hexanoic acid 2,5-dioxo-pyrrolidin-1-yl ester in anhydrous tetrahydrofuran was added. The reaction mixture was then stirred, preferably for 1 hour. The mixture was acidified (by adding 0.1% trifluoroacetic acid (TFA) in water (2 ml)). The reaction was followed by HPLC. The reaction mixture was concentrated and purified by

chromatography to obtain polypeptide-**oligomer conjugate**
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DEFINITIONS - Preferred Definitions:
R2 = fatty acid moiety or its ester comprising 0-5C alkyl;
R1 = methyl.

L115 ANSWER 7 OF 21 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-210063 [20] WPIX
DNC C2003-053448
TI Monodispersed mixture of **conjugates** useful in the treatment of bone disorders e.g. osteoporosis, comprises calcitonin drug coupled to an **oligomer** containing polyethylene glycol.
DC A25 A96 B04
IN ANSARI, A M; EKWURIBE, N N; ODENBAUGH, A L; PRICE, C H
PA (ANSA-I) ANSARI A M; (EKWU-I) EKWURIBE N N; (ODEN-I) ODENBAUGH A L; (PRIC-I) PRICE C H; (NOBE-N) NOBEX CORP
CYC 101
PI WO 2002098451 A1 20021212 (200320)* EN 63 A61K038-23 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
US 2003060606 A1 20030327 (200325) A61K038-23 <--
US 6713452 B2 20040330 (200423) A61K038-23 <--
EP 1404360 A1 20040407 (200425) EN A61K038-23 <--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
KR 2004004694 A 20040113 (200434) A61K038-23 <--
ADT WO 2002098451 A1 WO 2002-US17575 20020604; US 2003060606 A1 US 2001-873777 20010604; US 6713452 B2 US 2001-873777 20010604; EP 1404360 A1 EP 2002-732030 20020604, WO 2002-US17575 20020604; KR 2004004694 A KR 2003-715912 20031204
FDT EP 1404360 A1 Based on WO 2002098451
PRAI US 2001-873777 20010604
IC ICM **A61K038-23**
ICS C07C043-11; **C07K014-585**; C08G063-54
AB WO 200298451 A UPAB: 20030324
NOVELTY - A monodispersed mixture of **conjugates** comprises a calcitonin drug coupled to an **oligomer** (a) containing polyethylene glycol (b).
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for synthesizing a monodispersed mixture of **conjugates** involving:
(1) reacting a monodispersed mixture containing compounds of formula R1(OC2H4)m-O-X+ (I) with a monodispersed mixture comprising compound of formula R2(OC2H4)n1-OMs (II) to provide a monodispersed mixture comprising polymers of formula R2(OC2H4)m+n1-OR1 (III);
(2) activating (III) to provided a monodispersed mixture of activated polymers capable of reacting with calcitonin drug;
(3) and reacting the monodispersed mixture of activated polymers with a monodispersed mixture of drugs to provide a monodispersed mixture of **conjugates** comprising calcitonin drug coupled to an **oligomer** containing polyethylene glycol with m+n1 subunits.
R1, R2 = H or lipophilic moiety;
m, n1 = 1-25;
X+ = positive ion.
ACTIVITY - Osteopathic; Cytostatic.
Salmon calcitonin (150 mg) was dissolved in dimethylformamide (30 ml). TEA (35 micro l) and activated CH3(O-CH2-CH2)8-(CH2)5-C(O)-O-(CH2)7-pyrrolidone-2,5-dione-1-yl (42 mg) in anhydrous tetrahydrofuran (2 ml) was

added. The reaction was stirred for 1 hour, quenched with 0.1% trifluoroacetic acid in water (2 ml). The reaction was followed by HPLC. The reaction mixture was concentrated and purified to obtain PEG7-octyl-sCT, mono and **diconjugates.** Male CF-1 mice were distributed into groups of five animals per time point and were administered a single oral dose of a PEG7-octyl-(sCT), **diconjugate** (Octyl Di) (test) or salmon calcitonin (sCT or Calcitonin) for comparison. Oral doses were administered at 10 ml/kg in a phosphate-buffered PEG7-octyl-sCT, **diconjugate** formulation. The buffered formulation was prepared by adding sodium cholate to phosphate buffer (80 mL). The deoxy cholate was then added and stirred. The PEG7-octyl-sCT, **diconjugate**, solution was added. The remaining phosphate buffer was added to achieve a final weight of 100 g. Dose-response curves were constructed. At appropriate time points, mice were anesthetized, the vena cavae exteriorized, and blood samples were obtained. Blood aliquots were clotted at 22 deg. C for 1 hour, and the sera removed and pipetted into a clean receptacle. Total serum calcium was determined for each animal. Serum calcium data were plotted and pharmacokinetic parameters determined. The % baseline calcium drop at 2 micro g/kg dose for the test was 21%. The in vitro activity of PEG7-octyl-sCT and PEG7-decyl-sCT mono- and **diconjugates**, the stearate-PEG6-sCT, **diconjugate**, and stearate-PEG8-sCT, **diconjugate**, appeared to have in vivo activity that was comparable with the in vivo activity observed for the PEG7-octyl-sCT and PEG7-decyl-sCT, mono and **diconjugates.** The improved in vivo activity of the stearate containing **conjugates** indicated that these **conjugates** were undergoing hydrolysis in vivo to provide an active salmon calcitonin or active salmon calcitonin-PEG **conjugate.** ,

MECHANISM OF ACTION - None given.

USE - The mixture is used in the treatment of bone disorders e.g. excessive osteoclastic bone resorption or hypercalcemic serum effects, osteoporosis, Paget's disease and hypercalcemia in a subject, and for accelerating the growth rate of an animal (claimed). It is also used in the treatment of osteoporosis and non-healing fractures.

ADVANTAGE - The mixture has capability of lowering serum calcium level by at least 5, especially at least 20%. The mixture has increased resistance to degradation by chymotrypsin when compared to a calcitonin drug, which is not coupled to the **oligomer.** The mixture has a bioefficacy is also greater. The mixture has inter-subject variability that is less than the inter-subject variability of a polydispersed mixture of calcitonin drug-**oligomer conjugates** having same number average molecular weight as the mixture.

Dwg.0/18

FS CPI

FA AB; DCN

MC CPI: A12-V01; B04-C01G; B04-C03C; B04-N02A; B14-N01

TECH UPTX: 20030324

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Mixture: A preferred monodispersed mixture of **conjugates** comprises a salmon calcitonin drug coupled at Lys11 of the salmon calcitonin to the carboxylic acid moiety of carboxylic acid, which is covalently coupled at the end distal to the carboxylic acid moiety to a methyl terminated polyethylene glycol having at least 7 polyethylene glycol subunits and covalently coupled at Lys18 of the salmon calcitonin to the carboxylic acid moiety of a carboxylic acid, which is covalently coupled at the end distal to the carboxylic acid moiety to a methyl terminated polyethylene glycol moiety having at least 7 polyethylene glycol subunits

TECHNOLOGY FOCUS - POLYMERS - Preferred Components: The mixture having at least 4 polyethylene glycol subunits has molecular weight distribution with a standard deviation of less than 22 (preferably less than 14, especially less than 11) Daltons. (b) has at least 2, 3 or 4 (preferably at least 5 or 6, especially at least 7) polyethylene glycol subunits. The polyalkylene glycol is polypropylene glycol. The polypropylene glycol is

uniform. The mixture of **conjugates** has a dispersity coefficient greater than 10000 (preferably 100000, especially 500000). When each **conjugate** is same in the mixture, each **conjugate** has the formula Calcitonin Drug-(B'-Lh-Gi-Rm'-G'j-R'n'-Qk-T)p.
B' = bonding moiety (preferably carbonyl);
L = linking moiety;
G, G', Q = spacer moiety;
R = lipophilic moiety or polyalkylene glycol (preferably polyethylene glycol having 7 polyethylene glycol subunits);
R' = R (preferably 7-16C alkylene);
T = terminating moiety (preferably methyl or methoxy);
h, i = 0-1;
j = 0-1 (preferably 1);
k, n, m = 0-1 (preferably 0); and
p = 1 - number of nucleophilic residues on the drug;
Preferred **Oligomer**: (a) is covalently coupled to an amine function of the salmon calcitonin. (a) further comprises a lipophilic moiety covalently coupled to the second polyethylene glycol. The calcitonin drug is covalently coupled to the lipophilic moiety. The polyethylene glycol is covalently coupled to the lipophilic moiety. (a) comprises a first polyethylene glycol moiety covalently coupled to the calcitonin drug by a non-hydrolyzable bond and a second polyethylene glycol covalently coupled to the first polyethylene glycol moiety by a hydrolyzable bond.

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: The calcitonin drug is salmon calcitonin. The amino function is at Lys18 or Lys18 of the salmon calcitonin. The first **oligomer** is coupled to Lys11 of the salmon calcitonin and the second is covalently couple to Lys18 of the salmon calcitonin. The calcitonin drug is covalently coupled to the polyethylene glycol moiety of the **oligomer** by hydrolyzable bond.
Preferred **Conjugates**: The **conjugate** comprises several **oligomers** having same molecular structure. The **conjugate** comprises a first **oligomer** and a second **oligomer.** The **conjugate** is **amphiphilically** balanced such that the **conjugate** is aqueously soluble and able to penetrate biological membrane. The **conjugate** in the mixture comprises salmon calcitonin coupled at Lys11 to a first **oligomer** and coupled at Lys18 to a second **oligomer** or each **conjugate** in the mixture comprises salmon calcitonin coupled at Lys11 or Lys18 to an **oligomer** of formula C(O)(CH2)9(OC2H4)7OCH3. The first **oligomer** and the second **oligomer** have formula C(O)(CH2)7(OC2H4)7OCH3 or C(O)(OCH2CH2)6OC(O)(CH2)16CH3.
Preferred Process: The synthetic method further involves:
(1) reacting a monodispersed mixture comprising compounds of formula R2(OC2H4)n1OH (V) with a methanesulfonyl chloride to provide a monodispersed mixture comprising (II);
(2) reacting a monodispersed mixture comprising compounds of formula R2OMs (VI) with a monodispersed mixture comprising compounds of formula R3(OC2H4)mO- X+2 (VII) to provide a monodispersed mixture comprising compounds of formula R3(OC2H4)mOR2 (VIII);
(3) reacting (VIII) to provide a mixture comprising (V); or
(4) reacting a monodispersed mixture comprising a compound of formula R1(OC2H4)n1-OH (IV) to provide (I).
The activating of the mixture involves reacting (III) with N-hydroxy succinimide to provide an activated polymer capable of reacting with calcitonin drug. The reaction of monodispersed mixture of activated polymers with a monodispersed mixture of salmon calcitonin involves reacting the monodispersed mixture of activated polymers with Lys11 and Lys18 of the salmon calcitonin to provide monodispersed mixture of **monoconjugates** each comprising human calcitonin coupled to an **oligomer** containing polyethylene glycol with m+n1 subunits.

R3 = benzyl, trityl or THP;
X+2 = positive ion.

ABEX UPTX: 20030324

ADMINISTRATION - Administration is oral, rectal, topical, by inhalation (by aerosol), buccal (e.g. sublingual), vaginal, parenteral (including subcutaneous, intramuscular, intradermal, intraarticular, intrapleural, intraperitoneal, intracerebral, intraarterial or intravenous), transdermal or topical. Dosage is 10 mg-100 g, preferably 10-50 mg/kg for oral administration and 0.5-5 mg/kg for intramuscular injection.
EXAMPLE - Salmon calcitonin (150 mg) was dissolved in dimethylformamide (30 ml). TEA (35 microl) and activated CH3(O-CH2-CH2)8-(CH2)5-C(O)-O-(CH2)7-pyrrolidone-2,5-dione-1-yl (42 mg) in anhydrous tetrahydrofuran (2 ml) was added.. The reaction was stirred for 1 hour, quenched with 0.1% trifluoroacetic acid in water (2 ml). The reaction mixture was concentrated and purified to obtain PEG7-octyl-sCT, mono and **diconjugates.**

DEFINITIONS - Preferred Definitions:
R2 = fatty acid moiety or its ester comprising 0-5C alkyl;
R1 = methyl.

L115 ANSWER 8 OF 21 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-210058 [20] WPIX
DNC C2003-053443
TI Monodispersed mixture of **conjugates** useful in the treatment of diabetes comprises an insulin drug coupled to an **oligomer** containing a polyethylene glycol moiety.
DC A25 A96 B04
IN ANSARI, A M; EKWURIBE, N N; ODENBAUGH, A L; PRICE, C H; RADHAKRISHNAN, B
PA (ANSA-I) ANSARI A M; (EKWU-I) EKWURIBE N N; (ODEN-I) ODENBAUGH A L; (PRIC-I) PRICE C H; (RADH-I) RADHAKRISHNAN B; (NOBE-N) NOBEX CORP
CYC 101
PI WO 2002098232 A1 20021212 (200320)* EN 64 A01N061-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
US 2003027748 A1 20030206 (200320) A61K038-28 <--
BR 2001006851 A 20030408 (200329) A61K038-28 <--
JP 2003113113 A 20030418 (200335) 182 A61K038-28 <--
EP 1404178 A1 20040407 (200425) EN A01N061-00
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
KR 2004004692 A 20040113 (200434) A61K038-28 <--
ADT WO 2002098232 A1 WO 2002-US17574 20020604; US 2003027748 A1 US 2001-873899 20010604; BR 2001006851 A BR 2001-6851 20011011; JP 2003113113 A JP 2001-316998 20011015; EP 1404178 A1 EP 2002-737359 20020604, WO 2002-US17574 20020604; KR 2004004692 A KR 2003-715910 20031204
FDT EP 1404178 A1 Based on WO 2002098232
PRAI US 2001-873899 20010604
IC ICM A01N061-00; **A61K038-28**
ICS A01N037-18; A61K031-00; **A61K038-00**; A61K047-34; A61K047-48; A61P003-10; A61P005-50; **C07K014-62**
AB WO 200298232 A UPAB: 20030324
NOVELTY - A substantially monodispersed mixture of **conjugates** comprising an insulin drug coupled to an **oligomer** (a) containing a polyethylene glycol moiety (b), is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(1) a substantially monodispersed mixture of **conjugates**
(A') comprising human insulin covalently coupled at Lys-B29 of the human

insulin to the carboxylic acid moiety of a carboxylic acid, which is covalently coupled at the end distal to the carboxylic acid moiety to a methyl terminated polyethylene glycol having at least 7 polyethylene glycol subunits; and

(2) a method of synthesizing a monodispersed mixture of **conjugates** comprising:

(i) reacting a monodispersed mixture containing compounds of formula R1(OC2H4)m-O-X+ (I) with a substantially monodispersed mixture comprising compound of formula R2(OC2H4)n1-OMs (II) to provide a monodispersed mixture comprising polymers of formula R2(OC2H4)m+n1-OR1 (III);

(ii) activating (III) to provide a monodispersed mixture of activated polymers capable of reacting with insulin drug; and

(iii) reacting the monodispersed mixture of activated polymers with a monodispersed mixture of drugs to provide a monodispersed mixture of **conjugates** comprising insulin drug coupled to an **oligomer** containing polyethylene glycol with m+n1 subunits.

R, R2 = H or lipophilic moiety;

m, n1 = 1-25;

X+ = positive ion.

ACTIVITY - Antidiabetic.

MECHANISM OF ACTION - None given.

USE - The mixture is used in the treatment of insulin deficiency in a subject (claimed).

ADVANTAGE - The mixture exhibits greater in vivo/vitro activity than the in vivo/vitro activity of the polydispersed mixture of insulin drug-**oligomer conjugates** having same number of average molecular weight as the mixture respectively. The mixture has increased resistance to degradation by chymotrypsin when compared to the resistance to degradation by chymotrypsin of a polydispersed mixture of insulin drug-**oligomer conjugate** mixture having same number average molecular weight as the mixture. The mixture has inter-subject variability that is less than the inter-subject variability of a polydispersed mixture of insulin drug-**oligomer conjugates** having same number average molecular weight as the mixture.

Dwg.0/21

FS CPI

FA AB; GI; DCN

MC CPI: A12-V01; B04-C03C; B04-J03A; B14-S04

TECH UPTX: 20030324

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred **Conjugates**: The mixture has dispersity coefficient (DC) greater than 10000 (preferably greater than 100000, especially less than 500000) as given by a formula (i) or has molecular weight distribution with a standard deviation of less than 22 (preferably less than 14, especially less than 11) Daltons. The mixture has optionally same number of polyethylene glycol subunits. When each **conjugate** is same in the mixture, the each **conjugate** has formula Insulin Drug-(B'-Lh-Gi-Rm'-G'j-R'n'-Qk-T)p-. The **conjugate** is **amphiphilically** balanced such that the **conjugate** is aqueously soluble and able to penetrate biological membranes. At least 96, 97, 98 or 99% of the **conjugates** in the mixture has same molecular weight. In (A'), each **conjugate** comprises human insulin covalently coupled at Lys-B29 of the human insulin to the carboxylic acid moiety of hexanoic acid, which is covalently coupled at the end distal to the carboxylic acid moiety to a methyl terminated polyethylene glycol moiety having 7 polyethylene glycol subunits.

n = number of different molecules in the sample;

Ni = number of ith molecules in the sample;

Mi = mass of the ith molecule;

B' = bonding moiety (preferably carbonyl);

L = linking moiety;

G, G', Q = spacer moiety;

R' = lipophilic moiety or polyalkylene glycol (preferably polyethylene

glycol having 7 polyethylene glycol subunits);
R = lipophilic moiety or polyalkylene glycol (preferably 5C alkylene);
T = terminating moiety (preferably methoxy);
k, n', m' = 0-1 (preferably 0);
j = 0-1(preferably 1);
h, i = 0-1;
p = 1 - number of nucleophilic residues on the drug.
Preferred Components: The insulin drug is insulin (preferably human insulin) and the **oligomer** is covalently coupled to Lys-B29 of the human insulin and has formula -C(O)-(CH2)5-(OC2H4)7-OCH3.
The insulin drug is covalently coupled to the polyethylene moiety of the **oligomer** by hydrolyzable bond or to the lipophilic moiety.
Preferred Method: The method further involves:
(a) reacting a monodispersed mixture comprising compounds of formula R2(OC2H4)n1-OH (V) with a methanesulfonyl chloride to provide a monodispersed mixture comprising (II);
(b) reacting a monodispersed mixture comprising compounds of formula R2-OMs (VI) with a monodispersed mixture comprising compounds of formula R3(OC2H4)m-O- X+2 (VII) to provide a monodispersed mixture comprising compounds of formula R3(OC2H4)m-OR2 (VIII); and
(c) reacting (VIII) to provide a mixture comprising (V); or reacting a monodispersed mixture comprising a compound of formula R1(OC2H4)n1-OH (IV) to provide a substantially monodispersed mixture comprising (I).
R3 = benzyl, trityl or THP;
X+2 = positive ion.
The activating of the mixture involves reacting (III) with N-hydroxy succinimide to provide an activated polymer capable of reacting with insulin drug.
The reaction of monodispersed mixture of activated polymers with a monodispersed mixture of insulin involves reacting the monodispersed mixture of activated polymers with Lys-B29 of the human insulin to provide monodispersed mixture of **monoconjugates** each comprising human insulin coupled to an **oligomer** containing polyethylene glycol with m+n1 subunits.

TECHNOLOGY FOCUS - POLYMERS - Preferred Components: (b) has at least 2, 3 or 4 (preferably at least 5 or 6, especially at least 7) polyethylene glycol subunits.
Preferred **Oligomer**: (a) is covalently coupled to an amine function, which is at Lys-B29 of the insulin.
(a) comprises a first **oligomer** covalently coupled at Lys-B29 of the insulin and a second **oligomer** covalently coupled at N-terminal A1 or N-terminal B1 of the insulin.
The drug in synthesis method is a polypeptide.
(a) further comprises a lipophilic moiety optionally covalently coupled to the polyethylene glycol (preferably second polyethylene glycol).
The polyethylene glycol moiety is covalently coupled to the lipophilic moiety.
The first and the second **oligomers** are the same.
(a) comprises a first polyethylene glycol moiety covalently coupled to the insulin drug by a non-hydrolyzable bond and a second polyethylene glycol covalently coupled to the first polyethylene glycol moiety by a hydrolyzable bond.

ABEX UPTX: 20030324

ADMINISTRATION - The composition is administered in a dosage of 10 mg - 100 g orally, rectally, topically, by inhalation (by aerosol), buccally (such as sublingually), vaginally, parenterally (including subcutaneously, intramuscularly, intradermally, intraarticularly, intrapleurally, intraperitoneally, intracerebrally, intraarterially or intravenously), transdermally or topically. For oral administration the dosage is 10-50 mg/kg and for intramuscular injection the dosage is 0.5-5 mg/kg.
EXAMPLE - To human insulin in dimethylsulfoxide (25 ml) was added triethylamine (8 ml). The mixture was stirred for 5-10 minutes. Activated

oligomer 6-(2-(2-(2-(2-(2-(2-methoxyethoxy)ethoxy)-ethoxy)-ethoxy)-ethoxy)-ethoxy)-hexanoic acid 2,5-dioxo-pyrrolidin-1-yl ester in acetonitrile (7.5 ml) was added to the mixture under stirring. The solution was stirred for 45 minutes and quenched with acetic acid with maintaining the temperature below 27 degrees C. The mixture was monitored by HPLC. After work up, PEG-7-hexyl insulin **monoconjugate** at yield 40-60% was obtained. The crude mixture (PEG7-hexyl-insulin, **monoconjugate** 40-60%, unreacted insulin 8-25%, related substance 15-35%) was dialyzed. An animal model for evaluating formulations uses normal fasted dogs. The dog was given insulin **conjugates** to evaluate the efficacy of the formulation. The protocol for dog experiment cell for blood glucose measurement at time zero before a drug was administered. The oral liquid dosage formulation was then squirted into the back of the dog's mouth. Blood was drawn at 15, 30, 60 and 120 minutes and glucose levels were measured. The PEG7-hexyl-insulin **monoconjugate** showed less inter-subject variability and higher activity than the polydispersed PEG7-AVG-hexyl insulin.

DEFINITIONS - Preferred Definitions:
R2 = fatty acid moiety or its ester comprising 0-5C alkyl;
R1 = methyl.

L115 ANSWER 9 OF 21 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-167296 [16] WPIX
DNC C2003-043431
TI Monodispersed mixture of **conjugates** useful in the treatment of growth hormone deficiency, comprises growth hormone drug coupled to an **oligomer** containing polyalkylene glycol.
DC A25 A96 B04
IN ANSARI, A M; EKWURIBE, N N; ODENBAUGH, A L; PRICE, C H
PA (ANSA-I) ANSARI A M; (EKWU-I) EKWURIBE N N; (ODEN-I) ODENBAUGH A L; (PRIC-I) PRICE C H; (NOBE-N) NOBEX CORP
CYC 101
PI WO 2002098452 A1 20021212 (200316)* EN 73 A61K038-27 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
US 2003027995 A1 20030206 (200318) C07K014-61 <--
EP 1404361 A1 20040407 (200425) EN A61K038-27 <--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
KR 2004004693 A 20040113 (200434) A61K038-27 <--
ADT WO 2002098452 A1 WO 2002-US17504 20020604; US 2003027995 A1 US 2001-873757 20010604; EP 1404361 A1 EP 2002-737344 20020604, WO 2002-US17504 20020604; KR 2004004693 A KR 2003-715911 20031204
FDT EP 1404361 A1 Based on WO 2002098452
PRAI US 2001-873757 20010604
IC ICM **A61K038-27**; **C07K014-61**
ICS **C07K001-113**
AB WO 200298452 A UPAB: 20030307
NOVELTY - A substantially monodispersed mixture of **conjugates** comprises a growth hormone drug coupled to an **oligomer** containing a polyalkylene glycol moiety.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for synthesizing the substantially monodispersed mixture of **conjugates** involving:
(1) reacting a substantially monodispersed mixture containing compound of formula R1(OC2H4)m-O-X+ (I), with a substantially monodispersed mixture comprising a compound of formula R2(OC2H4)n1-OMs

(II) to provide a monodispersed mixture comprising polymers of formula R2(OC2H4)m+n1-OR1 (III);

(2) activating (III) to provide a monodispersed mixture of activated polymers capable of reacting with insulin drug; and

(3) reacting the monodispersed mixture of activated polymers with a monodispersed mixture of drugs to provide a monodispersed mixture of **conjugates** comprising insulin drug coupled to an **oligomer** containing polyethylene glycol with m+n1 subunits.

R1, R2 = H or lipophilic moiety;

m, n1 = 1-25;

X+ = positive ion.

ACTIVITY - Osteopathic.

MECHANISM OF ACTION - Growth hormone stimulator.

The activity of growth hormone (GH) GH-002 (test) was evaluated using transcription assay. Stable clones expressing the full-length human growth hormone receptor (GHR) were generated in 293 cells. A transcription assay was performed in 293 GHR cells transiently transfected with a reported construct containing stat5-binding element (LHRE) fused to a minimal TK promoter and luciferase. A beta -galactosidase expression vector was co-transfected as a transfection control and luciferase value corrected for beta -galactosidase activity. Sixteen hours after transfection, cells were transferred into serum free medium and treated with GH or agonist for 6 hours. Luciferase activity was reported as % of maximal activity stimulated by GH. Genotropin was used as the control. The mean fold induction by test was around 225 and for the control was around 25.

USE - The mixture is used in the treatment of growth hormone deficiency in a subject, and for accelerating the growth rate of an animal (claimed). It may also be used in the treatment of osteoporosis and non-healing fractures.

ADVANTAGE - The mixture exhibits greater in vivo activity than the in vivo activity of the polydispersed mixture of insulin drug-**oligomer conjugates** having same number of average molecular weight as the mixture. The mixture has increased resistance to degradation by chymotrypsin, and a lower inter-subject variability.

Dwg.0/30

FS CPI

FA AB; DCN

MC CPI: A05-H01B; A12-V01; B04-C03C; B04-J05J; B14-L01; B14-N01

TECH UPTX: 20030307

TECHNOLOGY FOCUS - POLYMERS - Preferred Components: The mixture has molecular weight distribution with a standard deviation of less than 22 (preferably less than 14, especially less than 11) Dalton or dispersity coefficient greater than 10000, especially 500000. In the mixture, the **oligomer** has optionally same number of polyalkylene glycol subunits. When each **conjugate** is the same in the mixture, each **conjugate** has a formula of Growth Hormone Drug-(B'-Lh-Gi-Rm'-G'j-R'n'-Qk-T)p-. The **conjugate** comprises several **oligomers**, which are same. The polyalkylene glycol moiety has at least 2, especially at least 7 polyalkylene glycol subunits. The polyalkylene glycol is uniform polypropylene glycol. The growth hormone drug is human growth hormone. The **oligomer** is covalently coupled to an amine function of the human growth hormone. The drug is covalently coupled to the **oligomer** optionally by a hydrolyzable bond or is coupled to the polyalkylene glycol moiety. The **oligomer** further comprises a lipophilic moiety covalently coupled to the polyalkylene glycol moiety and lipophilic moiety. The lipophilic moiety is covalently coupled to the second polyalkylene glycol moiety. The growth hormone drug is covalently coupled to the lipophilic moiety. The **oligomer** comprises a first polyalkylene glycol moiety covalently coupled to the growth hormone drug by a non-hydrolyzable bond and a second polyalkylene glycol covalently coupled to the first polyalkylene glycol moiety by a hydrolyzable bond. The **conjugate** is **amphiphilically** balanced such that the **conjugate** is aqueously soluble and able to penetrate

biological membranes. At least 96, 97, 98 or 99% of the **conjugates** in the mixture have the same molecular weight.
B' = bonding moiety;
L = linking moiety;
G, G', Q = spacer moiety;
R = lipophilic moiety or polyalkylene glycol (preferably polyalkylene glycol having at least 7 polypropylene glycol subunits);
R' = lipophilic moiety or polyalkylene glycol;
T = terminating moiety;
h, m' = 0-1;
i, k, n', j = 0-1 (preferably 0);
p = 1 - number of nucleophilic residues on the drug; and
n = number of different molecules in the sample.
Provided that when:
(1) R is polyalkylene glycol, m' is 1; and
(2) R' is polyalkylene glycol moiety, n' is 1.
Preferred Method: The method further involves:
(1) reacting a substantially monodispersed mixture comprising compounds of formula R2(OC2H4)n1-OH (V) with a methanesulfonyl chloride to provide a monodispersed mixture comprising (II);
(2) reacting a monodispersed mixture comprising compounds of formula R2-OMs (VI) with a monodispersed mixture comprising compounds of formula R3(OC2H4)m-O- X+2 (VII) to provide a monodispersed mixture comprising compounds of formula R3(OC2H4)m-OR2 (VIII);
(3) reacting (VIII) to provide a mixture comprising (V); and
(4) reacting a monodispersed mixture comprising a compound of formula R1(OC2H4)n1-OH (IV) to provide (I).
R3 = benzyl, trityl or THP;
X+2 = positive ion.
The activating of the mixture involves reacting the monodispersed mixture of formula (III) with N-hydroxy succinimide to provide an activated polymer capable of reacting with insulin drug. The reaction of the monodispersed mixture of activated polymers with a monodispersed mixture of human growth hormone involves reacting the monodispersed mixture of activated polymers with amino function of amino acid residue of human growth hormone selected from Phe1, Lys38, Lys41, Lys70, Lys115, Lys140, Lys145, Lys158, Lys168 or Lys172 to provide monodispersed mixture of **monoconjugates** each comprising human insulin coupled to an **oligomer** containing polyethylene glycol with m+n1 subunits.

ABEX UPTX: 20030307

ADMINISTRATION - Administration is oral, rectal, topical, by inhalation (by aerosol), buccal (such as sublingual), vaginal, parenteral (e.g. subcutaneous, intramuscular, intradermal, intraarticular, intrapleural, intraperitoneal, intracerebral, intraarterial or intravenous), transdermal or topical. Dosage is 10 mg-100 g, preferably 10-50 mg/kg for oral administration and 0.5-5 mg/kg for intramuscular administration.
EXAMPLE - Non-dispersed activated hexaethylene glycol monomethyl ether was prepared analogous to non-polydispersed triethylene glycol. A 20% phosgene in toluene solution was chilled under N2 atmosphere in ice/salt water bath. Non-polydispersed hexaethylene glycol was dissolved in anhydrous EtOAc (5 ml) and added to the phosgene solution. The mixture was stirred in ice bath for 1 hour, removed and stirred for 2.5 hours at room temperature. The phosgene, EtOAc and toluene were removed. The non-polydispersed residue (CH3(OC2H4)6-O-C(O)Cl) was dissolved in dry dichloromethane (20 ml) and placed under inert atmosphere. Triethylamine and then N-hydroxy succinimide (NHS) were added and the mixture was stirred at room temperature for 18 hours. The mixture was filtered. After work up, UV active non-polydispersed NHS ester (CH3(OC2H4)6O-C(O)-O-pyrrolidin-2,5-dion-1-yl) was obtained. Human growth hormone (hGH) was dissolved in dimethyl sulfoxide. Triethylamine was added and the solution was stirred for 10 minutes. The non-polydispersed activated hexaethylene glycol (2 equivalents or 5 equivalents) was added from a activated **oligomer** in dry tetrahydrofuran. Reaction was stirred for 45

minutes at room temperature. Aliquots were quenched in 0.1% trifluoroacetic acid in water. HPLC analysis was carried for comparison of the 2 polymer equivalent and the 5-polymer equivalent reaction mixture versus **unconjugated** hGH. Samples of the **conjugates** were purified. The entire peak from the 2 reaction mixtures was collected. The mass spectra of the material showed presence of mono-**conjugated**, di-**conjugated**, tri-**conjugated** and tetra-**conjugated** hGH as well as some remaining hGH. The 5 equivalent reaction mixture was purified. MALDI mass spectra of the concentrated fractions indicated that the level of **conjugation** of the protein increased with retention time.

DEFINITIONS - Preferred Definitions:
R2 = fatty acid moiety or its ester comprising at least 5C alkyl;
R1 = methyl.

L115 ANSWER 10 OF 21 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-046722 [04] WPIX
DNC C2003-011825
TI Treatment of diabetes mellitus using an insulin-polypeptide derivative.
DC A96 B04
IN EKWURIBE, N N; FILBEY, J A; PRICE, C H; STILL, J G; ANSARI, A M; ODENBAUGH, A L; RADHAKRISHNAN, B
PA (EKWU-I) EKWURIBE N N; (FILB-I) FILBEY J A; (PRIC-I) PRICE C H; (STIL-I) STILL J G; (NOBE-N) NOBEX CORP
CYC 101
PI WO 2002065985 A2 20020829 (200304)* EN 114 A61K000-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
US 2003050228 A1 20030313 (200321) A61K038-28 <--
AU 2002244020 A1 20020904 (200427) A61K000-00
EP 1409006 A2 20040421 (200427) EN A61K038-28 <--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
ADT WO 2002065985 A2 WO 2002-US4440 20020214; US 2003050228 A1 Provisional US 2001-269198P 20010215, US 2002-75097 20020213; AU 2002244020 A1 AU 2002-244020 20020214; EP 1409006 A2 EP 2002-709541 20020214, WO 2002-US4440 20020214
FDT AU 2002244020 A1 Based on WO 2002065985; EP 1409006 A2 Based on WO 2002065985
PRAI US 2002-347713P 20020111; US 2001-269198P 20010215; US 2002-75097 20020213
IC ICM A61K000-00; **A61K038-28**
ICS **C07K014-62**
AB WO 200265985 A UPAB: 20030117
NOVELTY - Treatment of diabetes mellitus comprises orally administering an insulin-polypeptide derivative (I) to a patient within one hour of ingestion of a meal so that it provides an insulin drug concentration in portal vein blood between 10 and 1,000 U/ml within about 60 minutes of administration .

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for the use of (I) in the manufacture of an oral medicament for the treatment of diabetes mellitus.

ACTIVITY - Antidiabetic.

Pancreactomized and normal, fasted dogs were orally administered with a polydispersed mixture of insulin polypeptide -NH-C(O)-(CH2)5(OC2H4)7OCH3 (1 mg/kg). At the given dosage of the insulin, all the dogs required glucose rescue, due to marked symptomatic hypoglycemia.

MECHANISM OF ACTION - None given.
USE - In the treatment of diabetes mellitus (claimed).
ADVANTAGE - (I) provides an insulin drug concentration in portal vein blood from about 10 - 1000 U/ml in about 60 (preferably 30) minutes of administration; provides maximum insulin drug concentration in peripheral blood in about 60 minutes; stabilizes peripheral glucose concentration to plus or minus 50% of average peripheral glucose concentration in 30 - 60 minutes; clears the bloodstream of a patient in about 4 hours; and reduces hepatic glucose production in a patient by at least 25% in about 90 minutes. At least 25% of post-prandial glucose resulting from ingestion of a meal by the patient is hepatically absorbed in about 120 minutes after injection of the meal (all claimed).
Dwg.1a/20

FS CPI
FA AB; GI; DCN
MC CPI: A12-V01; B04-C03C; B04-J03A; B14-S04
TECH UPTX: 20030117
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Components: (I) is an insulin polypeptide-**oligomer conjugate** (preferably **amphiphilically**-balanced insulin polypeptide-**oligomer conjugate** (II)), an insulin analog. The **oligomer** is coupled to the lysine at the B29 position of the insulin. The insulin analog is Gly-A21, Gly-A21 Gln-B3, Ala-A21, Ala-A21 Gln-B3, Gln-B3, Gln-B30, Gly-A21 Glu-B30, Gly-A21 Gln-B3 Glu-B30, Gln-B3 Glu-B30, Asp-B28, Lys-B28, Leu-B28, Val-B28, Ala-B28, Asp-B28 Pro-B29, Lys-B28 Pro-B29, Leu-B28 Pro-B29, Val-B28 Pro-B29 or Ala-B28 Pro-B29 human insulin.
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: (II) is present as a monodispersed mixture in a composition and is of formula insulin polypeptide-B'-Lj-Gk-R-G'm-R'-G''n-T (III) (preferably insulin polypeptide -NH-C(O)-(CH2)5(OC2H4)7OCH3).
B' = binding group (preferably ester, thio-ester, ether, carbamate, thio-carbamate, carbonate, thio-carbonate, amide or urea group or a covalent bond);
L = linker group (preferably alkyl or fatty acid group);
G, G' and G'' = spacer groups (preferably sugar, cholesterol or glycerine group);
R and R' = lipophilic group (preferably 1-28C (preferably 5-7C or 4-14C) alkyl or fatty acid group) or polyalkylene glycol group (preferably polyethylene glycol group containing 1 - 50 (preferably at least 2, especially 4 - 10) polyalkylene glycol subunits);
T = terminating group (preferably alkyl or alkoxy); and
j, k, m and n = 0 or 1.
ABEX UPTX: 20030117
ADMINISTRATION - Dosage of (I) is from 0.05 - 10 mg/kg body weight. (I) is administered orally 1 hour before, after or contemporaneously with a meal (all claimed).

L115 ANSWER 11 OF 21 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-001526 [01] WPIX
DNC C2003-000642
TI Polycation composition, e.g. useful for enhancing cell transfection, as a scaffold for cell growth and in printing and electronic coatings, comprises an **oligoamine** and a hydrophobic or **amphiphilic** group grafted to a polysaccharide chain.
DC A11 A96 B04 C03
IN DOMB, A J
PA (POLY-N) POLYGENE LTD
CYC 27
PI EP 1222926 A1 20020717 (200301)* EN 34 A61K031-715
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
US 2002146826 A1 20021010 (200301) C12N015-85
ADT EP 1222926 A1 EP 2002-250178 20020110; US 2002146826 A1 US 2002-44538

20020110
PRAI IL 2001-140844 20010110
IC ICM A61K031-715; C12N015-85
ICS A61K047-48; A61K048-00; C07H021-04; **C07K014-435**; C08B037-00; C08L005-00; C08L005-02
AB EP 1222926 A UPAB: 20030910
NOVELTY - New polycation composition (I) comprises:
(1) a polysaccharide chain;
(2) at least one **oligoamine** directly grafted to each 5 saccharide segment of the chain; and
(3) at least one further hydrophobic or **amphiphilic** group directly grafted to each 50 saccharide segment.
DETAILED DESCRIPTION - New polycation composition (I) comprises:
(1) a polysaccharide chain (having 2 to 2000 saccharide units);
(2) at least one **oligoamine** directly grafted to each 5 saccharide segment of the chain; and
(3) at least one further hydrophobic or **amphiphilic** group directly grafted to each 50 saccharide segment.
The **oligoamine** comprises linear, branched and cyclic amine having at least two amino groups.
The hydrophobic or **amphiphilic** group includes an aliphatic chain of at least 4 carbon atoms.
INDEPENDENT CLAIMS are also included for:
(1) a biodegradable polycation complex with a polyanion comprising (I) and an anionic polynucleic acid, protein or polysaccharide; and
(2) compositions containing (I).
USE - The composition is useful in combination with cationic and nonionic lipids or polymers for enhanced cell transfection. (I) is useful as a scaffold for cell growth and in non-medical coatings in the printing and electronic industry (claimed).
ADVANTAGE - (I) is not toxic or immunogenic.
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: A03-A01; A12-B01D; A12-V03; B04-C02; B04-E01; B04-N04; B10-B01B; C04-C02; C04-E01; C04-N04; C10-B01B
TECH UPTX: 20030910
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: The anionic macromolecule is preferably a plasmid, open chain polynucleic acid, **oligonucleotide**, antisense, peptide, protein and/or polysaccharide.
The polysaccharide chain is preferably a dextran, arabinogalactan, pullulan, cellulose, cellobios, inulin, chitosan, alginate or hyaluronic acid.
The saccharide units are preferably connected by an acetal, hemiacetal, ketal, orthoester, amide, ester, carbonate or carbamate bond.
The **oligoamine** is preferably of formula (II), a peptide with up to 20 amino acids (at least 50% of which are cationic including lysine, ornithine and arginine), spermine or an ethyleneimine **oligomer** having up to 10 ethyleneimine units. H2N-((CH2)x-NR-(CH2)y-NR'-(CH2)z)n-NH2 (II)
x, y, z = 0 - 4 and x+y+z = 1 - 4;
n = at least 1 when x+y+z is more than 1 or at least 2 when x+y+z = 1; and
R, R' = H or 1-6C aliphatic group.
The **amphiphilic** residue is preferably a fatty chain, phospholipid, cholesterol derivative, ethylene glycol **oligomer** and/or propylene glycol **oligomer** which facilitates crossing of the polycation through biological membranes.
The composition may further include a ligand for facilitating binding to a predetermined cell or tissue.
ABEX UPTX: 20030910
EXAMPLE - A solution of dialdehyde dextran (1g) in water (100ml) was added

over 5 hours to a solution of spermine (1.25g) in borate buffer (0.1M, pH11, 50ml) and the mixture was stirred for 24 hours. sodium borohydride (NaBH4) (1.0g) was added and the mixture was stirred for 48 hours. Additional NaBH4 (1.0g) was added and the mixture was stirred for 24 hours. The mixture was dialyzed against water (3 x 5000ml) at 4degreesC changing the water every 8 hours and the purified solution was filtered and freeze-dried to give 0.5g of dextran-spermine **conjugate.**

L115 ANSWER 12 OF 21 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-598046 [64] WPIX
CR 2001-049744 [06]; 2002-256788 [30]; 2004-095945 [10]; 2004-212164 [20]
DNC C2002-168856
TI Polymerization of alpha-amino acid N-carboxyanhydride monomers using amido-containing metallacycle initiator.
DC A96 B04
IN CURTIN, S A; DEMING, T J; HWANG, J; NOWAK, A; SEIDEL, S W; WYRSTA, M D; YU, M
PA (CURT-I) CURTIN S A; (DEMI-I) DEMING T J; (HWAN-I) HWANG J; (NOWA-I) NOWAK A; (SEID-I) SEIDEL S W; (WYRS-I) WYRSTA M D; (YUMM-I) YU M; (REGC) UNIV CALIFORNIA
CYC 1
PI US 2002032309 A1 20020314 (200264)* 44 C07K014-00 <--
US 6686446 B2 20040203 (200413) C07K001-00 <--
ADT US 2002032309 A1 Provisional US 1998-78649P 19980319, CIP of US 1999-272109 19990319, Provisional US 1999-133304P 19990510, Provisional US 1999-133305P 19990510, Provisional US 2000-187448P 20000307, Provisional US 2000-193054P 20000329, CIP of US 2000-568121 20000510, Provisional US 2000-210871P 20000608, US 2001-877957 20010608; US 6686446 B2 Provisional US 1998-78649P 19980319, CIP of US 1999-272109 19990319, Provisional US 1999-133304P 19990510, Provisional US 1999-133305P 19990510, Provisional US 2000-187448P 20000307, Provisional US 2000-193054P 20000329, CIP of US 2000-568121 20000510, Provisional US 2000-210871P 20000608, US 2001-877957 20010608
PRAI US 2001-877957 20010608; US 1998-78649P 19980319;
US 1999-272109 19990319; US 1999-133304P 19990510;
US 1999-133305P 19990510; US 2000-187448P 20000307;
US 2000-193054P 20000329; US 2000-568121 20000510;
US 2000-210871P 20000608
IC ICM **C07K001-00; C07K014-00**
ICS **C07K001-10**
AB US2002032309 A UPAB: 20040324
NOVELTY - Polymerization of alpha -amino acid N-carboxyanhydride (NCA) monomers comprises using an amido-containing metallacycle initiator comprising a nucleophilic alkyl amido group stabilized by a rigid chelate and a non-nucleophilic proton-accepting group selected from amido sulfonamidates, amido-amidates having an extracyclic nitrogen, amido-ureates, amido-carbamates and amido-aldimates.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a polyaminoacid chain comprising at least ten consecutive **oligo**(ethyleneglycol)-**conjugated** amino acid residues;

(2) an **amphiphilic** block copolypeptide comprising:

(a) a soluble block having at least 30 mol.% identical amino acid residues with charged or **oligo**(ethyleneglycol)-**conjugated** side chains; and

(b) an insoluble block comprising 60-100 mol.% nonionic amino acid residues;

(3) a chain-end functionalized block copolypeptide having ten or more consecutive identical amino acid residues and an end group selected from **oligosaccharides**, **oligonucleotides**, fluorescent molecules, polymer chains, small molecule therapeutic agents, or reactive chemical linkers for attaching the block copolypeptide to another molecule; and

(4) a chain-end functionalized block copolypeptide having ten or more consecutive identical amino acid residues and an end group selected from naphthyl, alkyl, allyl or cysteinamide.

USE - The products have potential applications in biomedical engineering, drug delivery, selective separation, biology, chemistry, physics, materials engineering, medicine (drug delivery, tissue engineering), smart hydrogels (environmentally responsive organic materials) and organic/inorganic biomimetic composites (artificial bone, high-performance coatings).

Dwg.0/7

FS CPI

FA AB; GI; DCN

MC CPI: A12-V01; B04-B03C; B04-C01; B04-C02X; B04-C03; B05-A03; B06-D01; B07-D03; B10-B02

TECH UPTX: 20021007

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - The initiator is preferably of formula (I):

X = SO2R4a, COR4a, C(O)X1R4a or C(R4a)=NR7a;

L = a Lewis base ligand;

M = a low valent transition metal;

R2a, R3a, R5a, R6a = H or organic substituents without highly protic or nucleophilic functionality;

R4a, R6a (sic) = organic substituents without highly protic or nucleophilic functionality;

X1 = O or NH;

R7a is not defined.

ABEX UPTX: 20021007

WIDER DISCLOSURE - Also disclosed are:

(i) production of an amido-containing metallacycle by combining an NCA monomer with an initiator comprising a low valent transition metal-Lewis base ligand complex; production of an initiator by combining an allyloxycarbonyl-protected amino acid amide and a low valent transition metal-Lewis base ligand complex;

(ii) 5- or 6-membered amido-containing metallacycles of formulae (A)-(D);

(iii) a method for adding an NCA to a polyaminoacid chain having an amido-containing metallacycle end group by combining the NCA with the polyaminoacid chain;

(iv) polymerization of NCA monomers with an initiator comprising a low valent transition metal-Lewis base ligand complex;

(v) production of block copolypeptides by combining a first NCA with an initiator comprising a low valent transition metal-Lewis base ligand complex and combining a second NCA with the resulting polyaminoacid chain;

(vi) block copolypeptide compositions having characteristics previously unattainable through conventional techniques;

(vii) production of **amphiphilic** block copolypeptides by combining an **oligo**(ethyleneglycol)-functionalized NCA with an initiator and combining the product with at least one other NCA;

(viii) vesicle-containing compositions comprising the **amphiphilic** block copolypeptides; and

(ix) production of EG-functionalized amino acid monomers by combining an ethylene glycol (EG) derivative with an amino acid having a reactive side group.

M = low valent transition metal;

L = Lewis base ligand;

R1-R3, R5, R6 = amino acid side chain selected from alanine, arginine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine or valine;

R4 = H or polyaminoacid chain; and

R7 = functional end group.

SPECIFIC COMPOUNDS - The initiator is a ruthenium complex of formula (Ia).

EXAMPLE - Polymerization of glutamic acid N-carboxyanhydride with a mixture of a p-cymene ruthenium N-tosyl-1,2-diphenylethylenediamine complex and 3 equivalents of trimethylphosphine in tetrahydrofuran gave a 95% yield of a polymer with a number-average molecular weight (Mn) of 12000.

L115 ANSWER 13 OF 21 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-280593 [32] WPIX
CR 2001-191346 [19]; 2001-514617 [56]; 2001-522432 [57]; 2003-040499 [03]
DNC C2002-082516
TI Preparing a red blood cell vehicle suitable for delivering an agent to a target site in a vertebrate due to loading the red blood cell with an agent-membrane translocation sequence.
DC B06 B07 D16
IN CRAIG, R
PA (GEND-N) GENDEL LTD; (CRAI-I) CRAIG R
CYC 97
PI WO 2002007752 A2 20020131 (200232)* EN 135 A61K038-16 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001072670 A 20020205 (200236) A61K038-16 <--
US 2002151004 A1 20021017 (200318) 144 C12N013-00 .
EP 1355656 A2 20031029 (200379) EN A61K038-16 <--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
ADT WO 2002007752 A2 WO 2001-GB3327 20010724; AU 2001072670 A AU 2001-72670 20010724; US 2002151004 A1 CIP of US 2000-748063 20001222, CIP of US 2000-748789 20001222, US 2001-785802 20010216; EP 1355656 A2 EP 2001-951821 20010724, WO 2001-GB3327 20010724
FDT AU 2001072670 A Based on WO 2002007752; EP 1355656 A2 Based on WO 2002007752
PRAI US 2001-785802 20010216; WO 2000-GB2848 20000724;
WO 2000-GB3056 20000809; WO 2001-GB417 20010201
IC ICM **A61K038-16**; C12N013-00
ICS A01K067-027; A61K009-50; A61K039-00; C12N005-08; C12N015-62
AB WO 200207752 A UPAB: 20031208
NOVELTY - Preparing a red blood cell vehicle (M1) suitable for delivering an agent to a target site in a vertebrate comprising providing a red blood cell and loading the red blood cell with an agent-MTS (membrane translocation sequence) **conjugate.**

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) delivering an agent (M2) to a target site in a vertebrate;

(2) a red blood cell vehicle suitable for delivery of an agent to a vertebrate, the red blood cell comprising agent-MTS **conjugate**;

(3) a kit comprising a red blood cell (I) prepared by (M2) and an agent comprising a membrane translocation sequence suitable for loading into the red blood cells and packaging materials;

(4) a pharmaceutical composition comprising a red blood cell prepared by M2 and a physiologically compatible buffer;

(5) loading (I) with an agent (M3) comprising exposing (I) to an agent-MTS **conjugate**;

(6) immunizing an animal with an antigen comprising M3 further comprising introducing (I) into a vertebrate and causing the agent to be released from the red blood cell;

(7) producing a red blood cell suitable for delivery of a polypeptide to a vertebrate (M4);

(8) delivering a polypeptide (M5) to a vertebrate; and

(9) producing a polypeptide agent-MTS **conjugate** (M6);

USE - The red blood cell produced by M4 may be used in the preparation of a medicament for delivery of an agent to or at a target site and of one or more agents to a vertebrate. The agent is actively released from the red blood cell vehicle by application of a stimulus to disrupt the red blood cell vehicle. The membrane translocation sequence is used in a method of delivery of an agent to a vertebrate by M2. (all claimed).

Dwg.0/19

FS CPI

FA AB; DCN

MC CPI: B04-B03B; B04-B03C; B04-C01; B04-E02H; B04-E03H; B04-E04; B04-E08; B04-E10; B04-E11; B04-F04; B04-F0400E; B04-N02; B04-N08; B04-P0100E; B11-C06; B11-C08B; B11-C09; B14-S11; D05-H07; D05-H12D5; D05-H12D6; D05-H14B2; D05-H16A; D05-H17A; D05-H17B; D05-H17C

TECH UPTX: 20020521

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: M2 preferably comprises:

(a) providing a red blood cell;

(b) loading the red blood cell with an agent-MTS **conjugate**;

(c) sensitizing the red blood cell to render it more susceptible to disruption than an unsensitised red blood cell;

(d) introducing the red blood cell into a vertebrate; and

(e) causing the agent-MTS **conjugate** to be released from the sensitised red blood cell by applying energy to the sensitised red blood cell.

M4 preferably comprises:

(a) providing a transgenic animal carrying and expressing a transgene encoding a fusion protein comprising the polypeptide and a MTS;

(b) obtaining a red blood cell containing the fusion protein from the animal; and

(c) sensitizing the red blood cell to render it susceptible to disruption by an energy source.

M5 preferably comprises:

(a) providing a transgenic animal carrying and expressing a transgene encoding a fusion protein comprising the polypeptide and a MTS;

(b) obtaining a red blood cell containing the fusion protein from the animal;

(c) sensitizing the red blood cell to render it susceptible to disruption by an energy source;

(d) introducing the sensitised red blood cell to a vertebrate; and

(e) exposing the vertebrate or part of it, to an energy source at a level sufficient to disrupt the sensitised red blood cell.

M6 preferably comprises:

(a) isolating a red blood cell from a transgenic animal carrying and expressing a transgene encoding a fusion protein comprising the polypeptide and a MTS;

(b) sensitizing the red blood cell to render it susceptible to disruption by an energy source;

(c) exposing the red blood cell to an energy source sufficient to disrupt the sensitised red blood cell; and

(d) isolating the fusion protein to provide the polypeptide agent-MTS **conjugate**.

Preferred Agent: The agent-MTS **conjugate** comprises a fusion protein in which the polypeptide is fused to a membrane translocation sequence enabling the agent to cross the plasma membrane of a cell. the membrane translocation sequence is selected from HIV-1-trans-activating protein (Tat), Drosophila Antennapedia homeodomain protein (Antp-HD), Herpes Simplex-1 virus VP22 protein (HSV-VP22), signal-sequence-based peptides, Transportan and **Amphiphilic** model peptide, homologues of them and their fragments variants and mutants having membrane translocational activity.

The agent-MTS-**conjugate** comprises the membrane translocation sequence

Gly Arg Lys Lys ArgArg Gln Arg Arg Arg Pro Pro Gln Cys
Arg Gln Ile Lys Ile Trp Phe Gln Asn Arg Arg Met Lys Trp Lys Lys
Arg Gln Ile Lys Ile Trp Phe Gln Asn Arg Arg Met Lys Trp Lys Lys Cys
The agent is selected from a protein, polypeptide, nucleic acid, **oligonucleotide**, peptide nucleic acid, virus-like particle, nucleotide, ribonucleotide, deoxyribonucleotide, modified deoxyribonucleotide, heteroduplex, nanoparticle, synthetic analogue of a ribonucleotide, modified nucleotide, modified ribonucleotide, amino acid, amino acid analogue, modified amino acid or analogue, steroid, proteoglycan, lipid or carbohydrate and mixtures, fusions, combinations or their **conjugates.**
The agent is fused to an imaging agent.
Preferred Cell: The red blood cell vehicle is sensitised by applying an electric field with a strength of 0.1kVolts/cm-10kVolts/cm under in vitro conditions, applying an electric pulse for between 1micros and 100ms or by exposure to diagnostic, therapeutic or a combination of ultrasound treatments at a power level of 0.05-100W/cm2 so that it is rendered more susceptible to disruption by exposure to a stimulus than an unsensitised red blood cell and is capable of being loaded with a larger amount of agent.
Preferred Polypeptide: The polypeptide is expressed under the control of a beta-globin promoter or enhancer, more preferably a beta-globin Locus Control Region (LCR).

ABEX UPTX: 20020521
EXAMPLE - No suitable example is given in the specification.

L115 ANSWER 14 OF 21 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-256788 [30] WPIX
CR 2001-049744 [06]; 2002-598046 [64]; 2004-095945 [10]; 2004-212164 [20]
DNC C2002-076395
TI Initiation of polymerization of an approximatelya-amino acid-N-carboxyanhydride (NCA) monomer useful for e.g. controlled polypeptide synthesis involves combining an NCA monomer with an amido-containing metallocycle.
DC A26 B04 D16 E12
IN CURTIN, S A; DEMING, T J; HWANG, J; NOWAK, A; SEIDEL, S W; WYRSTA, M D; YU, M
PA (REGC) UNIV CALIFORNIA
CYC 95
PI WO 2001094379 A2 20011213 (200230)* EN 108 C07K001-00 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001075409 A 20011217 (200230)
ADT WO 2001094379 A2 WO 2001-US18617 20010608; AU 2001075409 A AU 2001-75409 20010608
FDT AU 2001075409 A Based on WO 2001094379
PRAI US 2000-210871P 20000608
IC ICM **C07K001-00**
AB WO 200194379 A UPAB: 20040324
NOVELTY - In the initiation of an alpha -amino acid-N-carboxyanhydride (NCA) monomer polymerization an NCA monomer is combined with an initiator molecule (a). (a) contains amido-containing metallocycle having a nucleophilic alkyl amido group stabilized by a rigid chelate and a non-nucleophilic proton-accepting group (b).
DETAILED DESCRIPTION - Initiation of an alpha -amino acid-N-carboxyanhydride (NCA) monomer polymerization involves combining an NCA monomer with an initiator molecule (a). (a) contains amido-containing metallocycle having a nucleophilic alkyl amido group stabilized by a rigid chelate and a non-nucleophilic proton-accepting group (b). (b) is selected

from amido sulfonamide, amido-amidate having an extracyclic nitrogen, amido ureate, amido-carbamate or amido-aldimate.

INDEPENDENT CLAIMS are also included for the following:

(1) a polyamino acid chain comprising at least ten consecutive **oligo** (ethylene glycol)-**conjugated** amino acid residues;

(2) an **amphiphilic** block copolypeptide comprising a soluble block polypeptide and an insoluble block polypeptide. The soluble block comprises identical amino acid residues having charged (at least about 30 mole.%) or **oligo** (ethylene glycol)-**conjugated** side chains. The insoluble block comprises nonionic amino acid residues (about 60 - 100 mole.%);

(3) a chain-end functionalized block polypeptide having at least 10 consecutive identical amino acid residues. The end group is selected from **oligosaccharide**, **oligonucleotide**, fluorescent molecule, polymer, chain, small molecule therapeutic, or reactive chemical linker to attach the block copolypeptide to another molecule; and

(4) a chain-end functionalized block copolypeptide having an end group selected from a naphthyl, alkyl, allyl, or cysteinamide.

USE - For initiation of an amino acid-N-carboxyanhydride monomer polymerization (claimed) used for a variety of biomedical problems such as tissue engineering and drug delivery; for controlling both the structure and the properties of polypeptide materials; in incorporation of end group functionality onto the chains which is essential for targeting of the drug delivery complexes as well as substrate specific anchoring of these materials; in preparing complex polypeptide biomaterials which have potential applications in biology, chemistry, physics, and materials engineering. The potential application includes medicine (drug delivery, tissue engineering), smart hydrogels (environmentally responsive organic materials) and in organic/inorganic biomimetic composites (artificial bone, high performance coatings).

ADVANTAGE - The method allows successful peptide synthesis by using the versatile chemistry of transition metals to mediate the addition of monomers to the active polymer chain-ends and thus eliminate chain-breaking side reactions in favor of the chain-growth process. The method allows the formation of block copolymers and provides biochemical stability, self-assembly and water solubility into polypeptides.

Dwg.0/7

FS CPI

FA AB; GI; DCN

MC CPI: A02-A06; A05-F03; A05-J; A10-D03; B04-B03C; B04-C01; B04-C02X; B04-C03; D05-H18; E05-L; E05-M; E05-N; E10-A09B; E10-A10; E10-A20B; E10-B02; E10-G02

TECH UPTX: 20020513

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Initiator Molecule: (a) is of formula (VI), (VII), (VIII), (IX) or (X).

L = Lewis base ligand (preferably p-cymene);

M = low valent transition metal;

R2 and R6 = H or T (preferably H);

R3 and R5 = H or T (preferably phenyl);

T = any organic substituent not bearing free amine, hydroxyl, carboxylic acid, sulfhydryl, isocyanate, imidazole, other highly protic or nucleophilic functionality;

R4 = T;

ts = tosyl;

X = oxygen or NH;

Ph = phenyl.

Preferred Components: The nonionic amino acid residues are selected from phenylalanine, laucine, valine, isoleucine, alanine or methionine. The amino acid residues having charged side chains are selected from glutamic acid, aspartic acid, arginine, histidine, lysine, or ornithine. The amino acid residues having **oligo** (ethyleneglycol)-**conjugated** side chains are selected from EG-cysteine, EG-lysine, EG-serine, or EG-tyrosine.

TECHNOLOGY FOCUS - INORGANIC CHEMISTRY - Preferred Initiator molecule: (a) contains a low valent transition metal (preferably ruthenium).

TECHNOLOGY FOCUS - POLYMERS - Preferred Block: The insoluble block comprises copolypeptide (about 3 - 60 mole.%).

ABEX UPTX: 20020513

WIDER DISCLOSURE - The following are also disclosed. A (MI) method of making an amido containing metallocycle involving combining an NCA monomer with (a) comprising a low valent transition metal-Lewis base ligand complex to form an amido-containing metallocycle. A method (MII) of making an initiator molecule involving combining an alkyloxycarbonyl (alloc) protected amino acid amide and a low valent transition metal-lewis base ligand complex to form an amido-amidate metallocycle of formula (I):
R'1 and R'2 = amino acid side group or H;
R'3 = any functional end group capable of being attached to a primary amine group.
One of R'1 or R'2 is amino acid and the other is H.
Compositions (III) containing 5- or 6-membered amido-containing metallocycles of formula (II), (III), (IV) or (V).
R1, R2, R3, R5 and R6 = moiety selected from alanine, arginine, asparagine, aspartic acid, cystaine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine or valine;
R4 = H or polyaminoacid chain;
R7 = functional end group.
A method (MIII) of making a block copolypeptide involving combining a first NCA monomer with (a) comprising a low valent transition metal-Lewis base ligand complex to form a polyaminoacid chain and then combining a second NCA monomer with the polyaminoacid chain so that the second NCA monomer is added to the polyaminoacid chain. A method (MIV) of making an **amphiphilic** block copolypeptide involving generating a soluble block polypeptide by combining an **oligo**(ethylene-glycol)functionalized amino acid-N-carboxyanhydride (EG-aa-NCA) monomer with (a), and then attaching an insoluble block by combining the soluble block with a composition comprising at least one other amino acid NCA monomer. Also disclosed is a vesicle-containing composition comprising an **amphiphilic** block copolypeptide of NCA and water.

EXAMPLE - In a dry box, gamma-benzyl-L-glutamate-N-carboxyanhydride (Glu NCA) (50 mg) was dissolved in DMF (dimethylformamide) (1 ml) and placed in reaction tube. An aliquot of (S)-depeNiNHC(H)R1C(O)NR2 (where R1 = -CH2CH(CH3)2, R2 = -1-naphthyl) (C) (140 mul of a 14 mM solution in DMF) was added to the flask. A stir bar was added and the flask was sealed, removed from the dry box and stirred at 25degreesC in a thermostated bath for 24 hours. Polymer was isolated by adding reaction mixture to methanol containing HCl (1 mM) causing precipitation of the polymer. The polymer was dried in vacuo to obtain a white solid of poly(gamma-benzyl-L-glutamate) (19 mg).

L115 ANSWER 15 OF 21 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-082981 [11] WPIX
DNC C2002-025130
TI Derivatization of proteins comprises reacting proteins having at least two derivatizable pendant groups, with derivatizing reagent in presence of denaturant to provide protein derivative.
DC B04 D16
IN GREGORIADIS, G '; GREGORIADIS, G
PA (LIPO-N) LIPOXEN TECHNOLOGIES LTD; (GREG-I) GREGORIADIS G '
CYC 97
PI WO 2001087922 A2 20011122 (200211)* EN 19 C07K001-00 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU
SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2001058536 A 20011126 (200222) C07K001-00 <--
US 2003129159 A1 20030710 (200347) A61K038-16 <--
EP 1335931 A2 20030820 (200362) EN C07K001-107 <--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
RO SE SI TR
JP 2003533537 W 20031111 (200375) 24 C07K001-113 <--

ADT WO 2001087922 A2 WO 2001-GB2115 20010514; AU 2001058536 A AU 2001-58536 20010514; US 2003129159 A1 WO 2001-GB2115 20010514, US 2002-276552 20021118; EP 1335931 A2 EP 2001-931843 20010514, WO 2001-GB2115 20010514; JP 2003533537 W JP 2001-585141 20010514, WO 2001-GB2115 20010514

FDT AU 2001058536 A Based on WO 2001087922; EP 1335931 A2 Based on WO 2001087922; JP 2003533537 W Based on WO 2001087922

PRAI EP 2000-304108 20000516

IC ICM **A61K038-16**; **C07K001-00**; **C07K001-107**; **C07K001-113**

ICS **A61K038-00**; **A61K038-14**; A61P037-00; **C07K009-00**; **C07K014-62**; **C07K014-81**; **C07K016-18**; C08L089-00; C12N009-08

AB WO 200187922 A UPAB: 20020215

NOVELTY - Derivatization (M1) of proteins comprising reacting proteins (I) having at least two derivatizable pendant groups (being side chains of amino acyl units) with a derivatizing reagent (DR) in aqueous solution to provide a protein derivative, in the presence of an effective denaturing concentration of a denaturant, is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a protein compound (I) having at least 5 pendant polysialic acid chains, each having at least 5 sialic acid units joined to one another.

USE - (M1) is useful for derivatization of proteins (claimed).

ADVANTAGE - (M1) increases the degree of derivatization, whilst the protein retains activity, such as enzyme activity. The increase in the degree of derivatization enhances the increase in circulation time in vivo and stability on storage and in vivo. The labeled insulin, aprotinin and IgG, in their native forms, and derivatized with colominic acid (polysialic acid PSA) in the presence and absence of sodium dodecyl sulfate (SDS) are administered to mice to determine the rate of clearance from the circulation. The in vivo tests are carried out using standard methods, by injection of protein (in mg) which include insulin: native Ins (0.400), PSA:Ins (0.3960), and SDS/PSA:Ins (0.6640); aprotinin: native Apn (0.670), PSA:Apn (0.620), and SDS/PSA:Apn (0.770); and immunoglobulin G (IgG): native IgG (0.720), PSA:IgG (0.734), and SDS/PSA:IgG (0.726). The animals were bled from the tail vein immediately before and, immediately after, at 30 minutes, 1 hour, 4 hours, 6 hours, 12 hours, 24 and 48 hours after injection to determine the level of 125I label remaining in the circulation. From the logarithmic curve of percent initial radioactivity against time following injection, the area under the curve is determined. The results showed that derivatization of each protein with colominic acid resulted in an increase in the circulation time.

Dwg.0/4

FS CPI

FA AB; DCN

MC CPI: B04-C02; B04-C03; B04-N04; B10-A09A; D05-C12

TECH UPTX: 20020215

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Method: In (M1), the denaturant is an **amphiphilic** compound which is anionic, which include C8-24 alkyl sulfate monoester, preferably an alkali metal salt, more preferably sodium dodecyl sulfate, and is present at a concentration in the range 0.0001-0.01 M. The protein derivative is isolated from the denaturant, preferably in a recovery step involving dialysis, from a protein having at least 5 or 10 derivatizable groups, where the

derivatizable groups are all the same and are selected from hydroxyl, thiol, carboxylic acid and amine groups, and preferably all amine groups, especially epsilon amino groups of lysyl residues. (I) is preferably a therapeutically active compound. In (M1), the degree of substitution of the product is at least 2, preferably at least 5.

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Protein: In (I), the polysialic chains each having at least 10, preferably 20-50 mutually linked sialic acid units, are joined to the side-chains of non-terminal lysyl units through secondary amine linkages.

TECHNOLOGY FOCUS - POLYMERS - Preferred Reagent: DR is a polymeric compound, preferably selected from polyvinyl alcohol, polyethylene glycol preferably a monofunctional activated (polyethylene glycol), poly(hydroxyalkyl-(alk)acrylamides and -acrylates) and polysaccharide compounds, and a saccharide, which is an **oligo**- or polysaccharide, preferably a polysialic acid derivative, more preferably an aldehyde derivative of polysialic acid.

ABEX UPTX: 20020215

EXAMPLE - 24 mg of catalase with 50 mg of activated colominic acid, in the presence of 20 mg sodium cyanoborohydride in 5 ml potassium hydrogen phosphate buffer. The reactants were stirred at 35-40 degrees C. For a derivatization reaction carried out in the presence of sodium dodecyl sulfate (SDS), solid SDS was dissolved in the phosphate buffer to provide a final concentration of 1 x 10 to the power of -3 M SDS. After reaction times of 0 hours (i.e. as quickly as possible after the reaction mixture is made up), 6 hours, 12 hours, 24 hours and 48 hours, the reaction was stopped by addition of 70% ammonium sulfate solution to precipitate out protein. The precipitated mixture was cooled and stirred, then centrifuged. The supernatant was discarded and the pellet washed with saturated ammonium sulfate solution, spun again for 10 minutes at the same speed, and the supernatant discarded. The pellet was redissolved in 5 ml phosphate buffered saline. The resultant solution was dialyzed extensively at -4 degrees C against four changes of phosphate buffered saline. The solution was then passed down a Sephadex G-100 column and peaks collected and assayed for catalase and colominic acid content. The **conjugation** ratio (degree of substitution) of colominic acid with catalase in the presence and absence of SDS. The results showed that the presence of SDS increased the maximum **conjugation** ratio by a factor of about 3. The maximum level of derivatization in the presence of SDS appeared to be around 8 moles colominic acid per mole catalase. The derivatized catalase compounds were also tested against native catalase for their enzyme activity. The results showed the effect of subjecting catalase to the reaction conditions but without the addition of activated colominic acid. This showed that catalase activity was lost under those conditions, but that the loss of activity was inhibited by polysialylation. The inhibitor was greater when the polysialylation takes place in the presence of SDS.

L115 ANSWER 16 OF 21 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2001-559070 [63] WPIX
DNC C2001-166372
TI Encapsulation of an uncharged solid particle material to prepare capsule useful in pharmacy, involves treating the material with an **amphiphilic** substance and coating the material with a layers of a charged polyelectrolyte.
DC A96 A97 B07 C07 D13 D16 G05 P33
IN CARUSO, F; MOEHWALD, H; RENNEBERG, R; TRAU, D; MOHWALD, H
PA (PLAC) MAX PLANCK GES FOERDERUNG WISSENSCHAFTEN; (CARU-I) CARUSO F; (MOHW-I) MOHWALD H; (RENN-I) RENNEBERG R; (TRAU-I) TRAU D
CYC 28
PI EP 1116516 A1 20010718 (200163)* EN 23 B01J013-10
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT

RO SE SI
DE 10001172 A1 20010726 (200163) B01J013-02
WO 2001051196 A1 20010719 (200163) EN B01J013-10
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR
W: JP US
EP 1246692 A1 20021009 (200267) EN B01J013-10
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR
US 2002187197 A1 20021212 (200301) A01N037-18
JP 2003519565 W 20030624 (200341) 47 B01J013-04
ADT EP 1116516 A1 EP 2000-111523 20000529; DE 10001172 A1 DE 2000-10001172 20000113; WO 2001051196 A1 WO 2001-EP329 20010112; EP 1246692 A1 EP 2001-903643 20010112, WO 2001-EP329 20010112; US 2002187197 A1 WO 2001-EP329 20010112, US 2002-148890 20020617; JP 2003519565 W JP 2001-551606 20010112, WO 2001-EP329 20010112
FDT EP 1246692 A1 Based on WO 2001051196; JP 2003519565 W Based on WO 2001051196
PRAI DE 2000-10001172 20000113
IC ICM A01N037-18; B01J013-02; B01J013-04; B01J013-10
ICS A23P001-04; A61J003-07; A61K007-00; A61K009-127; A61K009-48; A61K009-50; A61K009-52; A61K031-56; **A61K038-00**; **A61K038-18**; A61K045-00; A61K047-12; A61K047-18; A61K047-20; A61K047-22; A61K047-24; A61K047-30; A61K047-32; A61K047-34; A61K047-36; A61K047-38; A61K047-42; A61P003-02; A61P005-00; A61P031-04; A61P043-00; B01J013-22; C08J007-04
AB EP 1116516 A UPAB: 20030915
NOVELTY - Encapsulation of an uncharged solid particle material, comprising treating the solid particle material with an **amphiphilic** substance, and subsequently coating the material with a layer of a charged polyelectrolyte or with a multilayer comprising alternating layers of oppositely charged polyelectrolytes, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) preparing capsules having a polyelectrolyte shell, comprising performing the novel method, and removing the core of the uncharged solid particles;

(2) a polyelectrolyte capsule, obtained by the novel method, or the method of (1); and

(3) a composition containing capsules in a dried form and having a monodisperse size distribution.

USE - For encapsulation of an uncharged solid particle material and for preparation of a capsule for the encapsulation of drugs and as reaction chambers. The capsule is useful in sensoric, surface-analytic or information technology applications and in pharmacy, medicine, food technology, biotechnology, cosmetics or in printing applications and as slow, targeted or controlled release systems. (All claimed).

ADVANTAGE - The drugs are released with a constant release rate and in small amounts over a long time period. The capsule thickness and permeability for the controlled release of the encapsulated material can be controlled in a predetermined manner.

Dwg.0/6
FS CPI GMPI
FA AB; DCN
MC CPI: A11-B05; A12-W05; B04-B03B; B04-B03C; B04-C02; B04-C02B; B04-C02D; B04-C02E3; B04-C03; B04-E01; B04-N04; B05-A01B; B10-A09A; B10-A22; B12-M10; B12-M11C; B14-B01; B14-R01; C04-B03B; C04-B03C; C04-C02; C04-C02B; C04-C02D; C04-C02E3; C04-C03; C04-E01; C04-N04; C05-A01B; C10-A09A; C10-A22; C12-M10; C12-M11C; C14-B01; C14-R01; D03-H01; D05-H09; D05-H19; G05-F
TECH UPTX: 20011031
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: The solid material has a low solubility in water or is water insoluble. The solid material is an organic material, a bio-material or an inorganic material. The solid material is selected from drugs, vitamins, nutrients, hormones,

growth factors, pesticides, antibiotics and/or preservatives. The solid material is selected from single crystals, amorphous or lyophilized materials, spray dried materials and/or milled materials. The solid material is a synthetic material or a material isolated from natural sources or a chemical modified isolated material. The **amphiphilic** substance is selected from ionic surfactant, preferably a cationic and/or an anionic surfactant, phospholipid or **amphiphilic** polyelectrolyte. The cationic surfactant is selected from quarternary ammonium salts, preferably didodecyldimethylammonium bromide, alkyltrimethylammoniumbromide, preferably dodecyltrimethylammonium bromide or palmithyltrimethylamonium bromide, and/or N-alkyl pyridinium salts, tertiary amine, preferably cholesteryl-3beta-N-(dimethyl-aminoethyl) carbamate, or secondary or primary amine. The anionic surfactant is selected from alkylsulfonate, preferably dodecylsulfate, laurylsulfate or olefinsulfonate, preferably sodium n-dodecylbenzenesulfonate, and/or alkylsulfates or fatty acids, preferably dodecanoic acid sodium salt or phosphoric acids or cholic acids or fluoro organics, especially lithium 3-(2-(perfluoroalkyl)ethylthio)propionate.
Preferred Process: The capsule thickness and permeability for the controlled release of the encapsulated material is controlled by the nature of the surfactant, the number of layers, the nature of the polyelectrolyte, the nature of the nanoparticle or biomolecule and an additional cross-linking step. The hollow capsules are produced from the encapsulated material by removal of the core material by exposure to an organic solvent in which the material is soluble or an acid and/or alkaline solvent in which the material is forming a soluble salt. The hollow capsules are re-dispersed in an aqueous solvent and/or an organic solvent. A drug is incorporated into the capsules. The size of pores within the capsule wall is controlled by the kind of **amphiphilic** substance used and/or the coating conditions of the **amphiphilic** substance. The capsule comprises no detectable residue of the solid core material and has a final shape, which is determined by the uncharged solid core material.

TECHNOLOGY FOCUS - POLYMERS - Preferred Components: The **amphiphilic** substance is a polymeric substance which provides charged groups and hydrophobic sides, preferably poly(styrenesulfonate), or is a block-copolymer, preferably poly(ethylethylene-blockstyrene sulfonic acid). The polyelectrolyte is selected from organic polymer, biopolymer and/or inorganic polymer or a block copolymer. The polyelectrolyte is a linear and/or a non-linear polymer. The organic polymer is selected from biodegradable polymers, preferably polyglycolic acid, polylactic acid, polyamides, poly-2-hydroxy butyrate, polycaprolactone, poly (lactic-co-glycolic) acid, fluorescent labelled polymer, conducting polymer, liquid crystal polymer, photo conducting polymer, photochromic polymer and/or their copolymers. The biopolymer is selected from polyamino acid, preferably peptide, S-layer protein, poly carbohydrate, preferably dextrin, pectin, alginate, glycogen, amylose, chitin, chondroitin, hyaluronic acid, poly nucleotide, preferably DNA or RNA, **oligonucleotide** and/or modified biopolymer, preferably carboxymethyl cellulose, carboxymethyl dextran or lignin sulfonate. The inorganic polymer is selected from polysilane, polysilanole, polyphosphazene, polysulfazene, polysulfide and/or polyphosphates.
Preferred Process: The polyelectrolyte is cross-linked after templating. The cross-linking is provided between the polymers in one layer and/or between the layers. The charged nanoparticles or biomolecules are deposited as capsule materials. The excessive material of **amphiphilic** substance, polyelectrolytes and/or nanoparticles and biomolecules, that are not contributed to form the coating, are separated after each coating step. The encapsulated material is forming a stable suspension in an aquatic phase.

ABEX UPTX: 20011031

EXAMPLE - An aqueous solution of poly(allylamine hydrochloride) (PAH) (500

mg) in water (6 ml) was adjusted to a pH of 8.1 with 1 M NaOH. An aqueous solution of fluorescein isothiocyanate (FITC) (4 mg) in dimethyl sulfoxide (DMSO) (500 micro-l) was added to the PAH solution. The mixture was incubated overnight at room temperature and then filtered. The **unconjugated** FITC was removed from the **conjugate** by gel filtration. The final fractions were dialyzed against deionized water overnight by using a slide-A-Lizer frame (Pierce) (0.5-2 ml) with a cut-off of molecular weight of 3500 Dalton. Yield of PAH-FITC solution was (25 ml) with a concentration of 9 mg/ml. A crystalline substance fluorescein diacetate and pyrene were milled. The substances (400 mg) were suspended in a 0.2 % sodium dodecylsulfate (SDS) solution (5 ml) by ultrasonification. The suspension was then stored unshaken for 2 hours at room temperature. A polyelectrolyte coating containing SDS, PAH (5 mg/ml solution of PAH in 0.5 M NaCl, pH 6), PSS (5 mg/ml solution of PSS in 0.5 M NaCl, pH 6), PAH, PSS and PAH-FITC (4.5 mg/ml solution of PAH-FITC in 0.25 M NaCl) was coated as layer one after another, incubated for 10 minutes at 12 degrees C. The excess of polyelectrolyte was removed by centrifugation. The treatment of the crystals with the SDS solution leads to a high negative surface charge. The resulting suspensions were highly stable and suitable as templates for the coating with polyelectrolytes. The yield of coated substance can be optimized to high rates (98 %).

L115 ANSWER 17 OF 21 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2001-496568 [54] WPIX
DNC C2001-149074
TI Compositions useful in treatment of obesity include luminal cholecystokinin releasing factor coupled to an **amphiphilic** polymer, which exhibits improved pharmacokinetic properties.
DC A25 A96 B04 D16
IN EKWURIBE, N N; EKWURIBE, N
PA (NOBE-N) NOBEX CORP; (EKWU-I) EKWURIBE N
CYC 95
PI WO 2001041812 A2 20010614 (200154)* EN 49 A61K047-48
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001020875 A 20010618 (200161) A61K047-48
BR 2000016339 A 20020827 (200265) A61K047-48
NO 2002002793 A 20020813 (200266) A61K000-00
EP 1237580 A2 20020911 (200267) EN A61K047-48
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
CZ 2002001990 A3 20021113 (200282) A61K047-48
KR 2002068053 A 20020824 (200309) A61K047-48
JP 2003516366 W 20030513 (200334) 59 A61K047-48
HU 2003000133 A2 20030528 (200341) A61K047-48
CN 1434725 A 20030806 (200366) A61K047-48
US 6638906 B1 20031028 (200372) A01N037-18
MX 2002005885 A1 20021101 (200376) A61K047-48
ZA 2002004603 A 20031126 (200402) 71 A61K000-00
NZ 519489 A 20040130 (200414) A61K047-48
US 2004092449 A1 20040513 (200432) A61K038-17 <--
ADT WO 2001041812 A2 WO 2000-US33592 20001211; AU 2001020875 A AU 2001-20875 20001211; BR 2000016339 A BR 2000-16339 20001211, WO 2000-US33592 20001211; NO 2002002793 A WO 2000-US33592 20001211, NO 2002-2793 20020612; EP 1237580 A2 EP 2000-984215 20001211, WO 2000-US33592 20001211; CZ 2002001990 A3 WO 2000-US33592 20001211, CZ 2002-1990 20001211; KR 2002068053 A KR 2002-707500 20020612; JP 2003516366 W WO 2000-US33592 20001211, JP 2001-543156 20001211; HU 2003000133 A2 WO 2000-US33592 20001211, HU 2003-133 20001211; CN 1434725 A CN 2000-818964 20001211; US

6638906 B1 US 1999-459443 19991213; MX 2002005885 A1 WO 2000-US33592 20001211, MX 2002-5885 20020612; ZA 2002004603 A ZA 2002-4603 20020607; NZ 519489 A NZ 2000-519489 20001211, WO 2000-US33592 20001211; US 2004092449 A1 Div ex US 1999-459443 19991213, US 2003-633966 20030804

FDT AU 2001020875 A Based on WO 2001041812; BR 2000016339 A Based on WO 2001041812; EP 1237580 A2 Based on WO 2001041812; CZ 2002001990 A3 Based on WO 2001041812; JP 2003516366 W Based on WO 2001041812; HU 2003000133 A2 Based on WO 2001041812; MX 2002005885 A1 Based on WO 2001041812; NZ 519489 A Based on WO 2001041812; US 2004092449 A1 Div ex US 6638906

PRAI US 1999-459443 19991213; US 2003-633966 20030804

IC ICM A01N037-18; A61K000-00; **A61K038-17**; A61K047-48
ICS A61P003-04; **C07K014-595**; C08G063-48; C08G063-91

AB WO 200141812 A UPAB: 20040210

NOVELTY - Compositions which include luminal cholecystokinin releasing factor (LCRF) coupled to **amphiphilic** polymers are new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) LCRF composition comprising LCRF coupled with one or more molecules of a non-naturally occurring polymer. The polymer comprises a **lipophilic** group and a **hydrophilic** polymer group, therefore imparting both **lipophilic** and **hydrophilic** characteristics to the composition so that the composition is soluble in pharmaceutical solvents and is able to interact with biological membranes;

(2) peptide composition comprising LCRF coupled with one or more molecules of a non-naturally occurring polymer which comprises a LM and a **hydrophilic** moiety. The composition is soluble in aqueous solvents and the LCRF is active in treatment or prevention of obesity;

(3) LCRF composition comprising LCRF covalently coupled with one or more molecules of a polymer which comprises a linear polyalkylene glycol group and a **lipophilic** group. The peptide and components are conformationally arranged such that the LCRF has an enhanced in vivo resistance to enzymatic degradation, relative to LCRF alone;

(4) multiligand **conjugated** LCRF complex comprising a triglyceride backbone group. The LCRF is covalently coupled with the triglyceride backbone group through a polyalkylene glycol spacer group which is bonded at a carbon atom of the triglyceride backbone. At least one fatty acid is covalently attached to a carbon atom of the triglyceride backbone group or is covalently joined through a polyalkylene glycol spacer group;

(5) stable, aqueous-soluble, **conjugated** LCRF complex which comprises a LCRF **conjugatively** coupled to a glycolipid group modified with polyethylene glycol;

(6) polysorbate complex comprising a polysorbate group which includes a triglyceride backbone which has a fatty acid group covalently coupled to one of the alpha , alpha ' or beta carbon atoms and a polyethylene glycol group covalently coupled to one of the alpha , alpha ' or beta carbon atoms. A physiologically active moiety can be covalently bonded to the polyethylene glycol group;

(7) compounds of formula (I):

X = N, O or S;

Y = LCRF or a protein;

n = 3 - 230; and

m = 0 - 20.

ACTIVITY - Anorectic. No biodata is provided.

MECHANISM OF ACTION - Luminal cholecystokinin releasing factor receptor agonist.

USE - The materials are useful for delivery of LCRF to receptors in the gut. LCRF is capable of stimulating release of cholecystokinin, a polypeptide hormone that induces satiety and reduces food intake. The materials may thus be used in treatment or prevention of obesity. Other peptides may be used in place of LCRF in the materials, so that they could be used for delivery of peptides useful in treatment of other disorders.

ADVANTAGE - The materials are stable and soluble in aqueous

solutions. They may exhibit prolonged blood circulation and can be conformationally arranged so that the LCRF has enhanced in vivo resistance to enzymatic degradation. The **conjugates** can also deliver LCRF to receptors in the gut without absorption into the bloodstream.
Dwg.0/3
FS CPI
FA AB; DCN
MC CPI: A10-E08; A12-V01; B04-C03D; B04-H01; B04-J13; B04-K01; B12-M05; B14-E12; B14-L01; D05-H10
TECH UPTX: 20010924
TECHNOLOGY FOCUS - POLYMERS - Preferred Polymer: The non-naturally occurring polymer has a molecular weight of 500-10,000 daltons. Typical **conjugates** include the compounds of formula (I) or polysorbate compounds which include a sorbitol component, a polyethylene glycol component and a fatty acid component. In the polysorbate compounds, the LCRF group is typically linked to a polyethylene glycol component via a carbamate bond.
ABEX UPTX: 20010924
ADMINISTRATION - Administration is, e.g., oral, parenteral, rectal, topical, vaginal, transdermal or nasal, especially oral or parenteral. Dosage is 10-1000 microg, preferably 50 microg-250 mg.

EXAMPLE - In a typical process for preparation of luminal cholecystokinin releasing factor (LCRF) **conjugates**, an **oligomeric** carboxylic alkanol is activated with bromine and esterified, then **oligomeric** polyethylene glycol is coupled to the activated alkane monomers. Coupling of the product to the free amino group of LCRF is achieved using N-hydroxysuccinimide in aqueous solution at a pH where the amino group is nucleophilic. Selectivity of the N-terminal amino group over the lysine side chain at residue 19 of LCRF is achieved by choosing the pH of the reaction medium. Coupling to the N-terminus is especially achieved at pH 9. By varying the relative length of the alkane (hydrophobic) and polyethylene glycol (**hydrophilic**) components, the **amphiphilicity** and solution structure of the **conjugated** can be optimized.

L115 ANSWER 18 OF 21 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2001-475649 [51] WPIX
CR 2000-587124 [55]; 2001-091750 [10]; 2001-244222 [25]; 2002-508310 [54]; 2002-556413 [59]; 2003-615989 [58]; 2003-678184 [64]; 2004-141477 [14]; 2004-178820 [17]; 2004-190101 [18]
DNC C2001-142565
TI Solid composition for delivery of active agents e.g. glyburide comprises carrier optionally containing a substrate having an encapsulation coat containing **hydrophilic** surfactants e.g. polyoxyethylene alkylethers.
DC A96 B05 B07
IN CHEN, F; PATEL, M V
PA (LIPO-N) LIPOCINE INC; (CHEN-I) CHEN F; (PATE-I) PATEL M V
CYC 95
PI WO 2001037808 A1 20010531 (200151)* EN 106 A61K009-14
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
US 6248363 B1 20010619 (200151) A61K009-16
AU 2001017981 A 20010604 (200153)
EP 1233756 A1 20020828 (200264) EN A61K009-14
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
US 2003064097 A1 20030403 (200325) A61K009-20

US 6569463 B2 20030527 (200337) A61K009-16
JP 2003517470 W 20030527 (200344) 118 A61K009-48
US 2003215496 A1 20031120 (200377) A61K009-48

ADT WO 2001037808 A1 WO 2000-US32255 20001122; US 6248363 B1 US 1999-447690 19991123; AU 2001017981 A AU 2001-17981 20001122; EP 1233756 A1 EP 2000-980761 20001122, WO 2000-US32255 20001122; US 2003064097 A1 Div ex US 1999-447690 19991123, US 2001-800593 20010306; US 6569463 B2 Div ex US 1999-447690 19991123, US 2001-800593 20010306; JP 2003517470 W WO 2000-US32255 20001122, JP 2001-539423 20001122; US 2003215496 A1 Div ex US 1999-447690 19991123, Cont of US 2001-800593 20010306, US 2003-428341 20030501

FDT AU 2001017981 A Based on WO 2001037808; EP 1233756 A1 Based on WO 2001037808; US 2003064097 A1 Div ex US 6248363; US 6569463 B2 Div ex US 6248363; JP 2003517470 W Based on WO 2001037808; US 2003215496 A1 Div ex US 6248363, Cont of US 6569463

PRAI US 1999-447690 19991123; US 2001-800593 20010306;
US 2003-428341 20030501

IC ICM A61K009-14; A61K009-16; A61K009-20; A61K009-48
ICS A61K009-02; A61K009-22; A61K009-28; A61K009-32; A61K009-46; A61K009-50; A61K009-51; A61K009-52; A61K009-54; A61K009-56; A61K009-58; A61K031-216; A61K031-232; A61K031-351; A61K031-366; A61K031-40; A61K031-404; A61K031-415; A61K031-4196; A61K031-421; A61K031-436; A61K031-4409; A61K031-4439; A61K031-4725; A61K031-522; A61K031-57; A61K031-64; A61K031-663; **A61K038-23**; A61K047-02; A61K047-10; A61K047-14; A61K047-22; A61K047-26; A61K047-28; A61K047-32; A61K047-36; A61K047-38; A61K047-44; A61P001-04; A61P003-04; A61P003-06; A61P003-10; A61P005-16; A61P005-24; A61P005-40; A61P007-02; A61P007-10; A61P009-04; A61P009-06; A61P009-10; A61P009-12; A61P013-08; A61P015-10; A61P017-12; A61P019-06; A61P019-10; A61P021-02; A61P025-04; A61P025-06; A61P025-08; A61P025-16; A61P025-20; A61P025-22; A61P025-26; A61P025-28; A61P029-00; A61P031-04; A61P031-10; A61P031-12; A61P033-06; A61P033-10; A61P035-00; A61P037-06; A61P043-00

AB WO 200137808 A UPAB: 20040426
NOVELTY - Composition for improved delivery of active agent comprising a solid carrier optionally containing a substrate having an encapsulation coat, where the solid carrier or encapsulation coat contains at least one active agent (I) and one **hydrophilic** surfactant (II), is new.

ADVANTAGE - The composition is used to deliver a wide variety of active agents having improved absorption and/or biovailability. It provides coated substrate materials without the need for binders. Prior art solid carriers are limited to a few specific drugs due to difficulties in formulating appropriate drug/exicipient compositions to effectively coat the active agent onto a carrier particle. Most of prior art solid dosage forms of **hydrophilic** active agents exhibit poor or no absorption of the active agent. Non-solid formulations of the same are chemically instable, leak and have capsule shell incompatibility. Conventional solid dosage forms of hydrophobic active agents often exhibit slow and incomplete dissolution and subsequent absorption. They often show a high propensity for biovariability and food interactions of the active agent, resulting in restrictive compliance/labeling requirements. A comparative dissolution study was performed on 3 forms of glyburide (Ia) namely coated beads of (Ia), commercially available (Ia) and pure (Ia) bulk. 5 mg Of each form was usd for triplication dissolution runs in 500 ml of isotonic pH 7.4 phosphate buffer.The dissolutiom medium was sampled at 15, 30, 45, 60, 120 and 180 minutes. The samples were filtered and the filtrates diluted for (Ia)-specific HPLC assay. The (Ia)-coated beads showed a superior dissolution profile in the rate, extent and variability of (Ia) dissolved/released into the medium.

Dwg.0/3

FS CPI

FA AB; DCN

MC CPI: A10-E08; A12-V01; A12-W12C; B01-C04; B01-D01; B01-D02; B03-H; B04-B01C1; B04-C02D; B04-C02X; B04-C03C; B04-D01; B04-N04; B05-B01P; B06-D05; B07-H; B10-A08; B10-A09A; B10-A09B; B10-A22; B10-C04D; B10-C04E; B12-M07; B12-M08; B12-M09; B12-M10; B12-M11

TECH UPTX: 20010910

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Composition: (I) is a drug, a nutrient, a cosmeceutical and/or a diagnostic agent. The substrate may be an additive and/or an active agent. (I) may be hydrophobic having an intrinsic aqueous solubility of less than 1 mg/ml. (I) may be **hydrophilic** with an apparent water solubility of at least 1 mg/ml. **Hydrophilic** (I) is selected from a drug, cytokine, peptidomimetic, peptide, protein, toxoid, serum, antibody, vaccine, nucleoside, nucleotide, genetic material and/or nucleic acid. The encapsulation coat further comprises at least one **lipophilic** additive selected from **lipophilic** surfactants and/or triglycerides. The composition is encapsulated, extruded, compressed, pelletized, coated, mixed, granulated, crystallized, Iyophilized or molded. It may be formulated as a capsule, a tablet, an ovule, a suppository, a wafer, a chewable tablet, a buccal tablet, a sub-lingual tablet, a quick-dissolve tablet, an effervescent tablet, a granule, a pellet, a bead, a pill, a sachet, a sprinkle, a film, a dry syrup, a reconstitutable solid, a suspension, a lozenge, a troche, an implant, a powder, a triturate, a platelet, or a strip. It may be formulated for immediate release, pulsatile release, controlled release, extended release, delayed release, targeted release, or targeted delayed release.

Preferred Substrate: The substrate is a powder or a multiparticulate. It may be an additive comprising a solubilizer, an enzyme inhibitor, an anti-adherent, an anticoagulant, an antifoaming agent, an antioxidant, a binder, a bufferant, a chelating agent, a coagulant, a colorants or opaquants, a coolant, a cryoprotectant, a diluent or filler, a disintegrant or super disintegrant, a hydrogen bonding agent, a flavorant or desensitizer, an ion-exchange resin, a plasticizer, a preservative, a solvent, a sweetener and/or a thickener. the substrate is a multiparticulate comprised of a granule, a pellet, a bead, a spherule, a beadlet, a microcapsule, a millisphere, a nanocapsule, a nanosphere, a microsphere, a platelet, a tablet or a capsule.

Preferred Carrier: The carrier is a bead, a beadlet, a granule, a spherule, a pellet, a microcapsule, a microsphere, a nanosphere, a film, a wafer, a sprinkle, an implant, a troche, a lozenge, a platelet, a nanocapsule or a strip. It is enteric coated, coated for fast disintegration, seal coated, film coated, barrier coated, compress coated, or coated with an enzyme-degradable coating.

Preferred **Lipophilic** Additive: The **lipophilic** additive is selected from alcohols, polyoxyethylene alkylethers, fatty acids, bile acids, glycerol fatty acid esters, acetylated glycerol fatty acid esters, lower alcohol fatty acids esters, polyethylene glycol fatty acids esters, polyethylene glycol glycerol fatty acid esters, polypropylene glycol fatty acid esters, polyoxyethylene glycerides, lactic acid derivatives of mono/diglycerides, propylene glycol diglycerides, sorbitan fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylenepolyoxypropylene block copolymers, transesterified vegetable oils, sterols, sterol derivatives, sugar esters, sugar ethers, sucroglycerides, polyoxyethylene vegetable oils, polyoxyethylene hydrogenated vegetable oils, reaction mixtures of polyols and at least one fatty acid, glyceride, optionally hydrogenated vegetable oils, and/or sterols. The triglyceride is selected vegetable oils, fish oils, animal fats, hydrogenated vegetable oils, partially hydrogenated vegetable oils, synthetic triglycerides, modified triglycerides, and/or fractionated triglycerides.

Preferred Surfactant: (II) is a non-ionic surfactant (IIa) having an **hydrophilic-lipophilic** balance (HLB) value of at least 10 or an ionic surfactant (IIb). (IIa) is selected from alkylglucosides, alkylmaltosides, alkylthioglucosides, lauryl macrogolglycerides,

polyoxyethylene alkyl ethers, alkylphenols, or sorbitan fatty acid esters, polyethylene glycol glycerol fatty acid esters, polyoxyethylene-polyoxypropylene block copolymers, polyglycerol fatty acid esters, polyoxyethylene glycerides, polyoxyethylene sterols, polyoxyethylene vegetable oils, polyoxyethylene hydrogenated vegetable oils and/or reaction mixtures of polyols and at least one fatty acid, glyceride, vegetable oil, hydrogenated vegetable oil, and sterol, tocopherol polyethylene glycol succinate, sugar ester, sugar ether and/or sucroglycerides. (IIb) is selected from alkyl ammonium salts, bile acids and their salts, or derivatives, fatty acid derivatives of amino acids, carnitines, **oligopeptides**, and polypeptides, glyceride derivatives of amino acids, **oligopeptides**, and polypeptides, acyl lactylates, mono-or diacetylated tartaric acid esters of mono- or diglycerides, succinylated monoglycerides, citric acid esters of mono- or diglycerides, alginate salts, propylene glycol alginate, optionally hydrogenated lecithins, optionally hydrogenated lysolecithins, lysophospholipids, phospholipids, alkylsulfate salts, fatty acid salts and/or sodium docusate.

TECHNOLOGY FOCUS - POLYMERS - Preferred Surfactant: (II) is a non-ionic surfactant (IIa) having an **hydrophilic-lipophilic** balance (HLB) value of at least 10 or an ionic surfactant (IIb). (IIa) is selected from alkylglucosides, alkylmaltosides, alkylthioglucosides, lauryl macrogolglycerides, polyoxyethylene alkyl ethers, alkylphenols, or sorbitan fatty acid esters, polyethylene glycol glycerol fatty acid esters, polyoxyethylene- polyoxypropylene block copolymers, polyglycerol fatty acid esters, polyoxyethylene glycerides, polyoxyethylene sterols, polyoxyethylene vegetable oils, polyoxyethylene hydrogenated vegetable oils and/or reaction mixtures of polyols and at least one fatty acid, glyceride, vegetable oil, hydrogenated vegetable oil, and sterol, tocopherol polyethylene glycol succinate, sugar ester, sugar ether and/or sucroglycerides. (IIb) is selected from alkyl ammonium salts, bile acids and their salts, or derivatives, fatty acid derivatives of amino acids, carnitines, **oligopeptides**, and polypeptides, glyceride derivatives of amino acids, **oligopeptides**, and polypeptides, acyl lactylates, mono-or diacetylated tartaric acid esters of mono- or diglycerides, succinylated monoglycerides, citric acid esters of mono- or diglycerides, alginate salts, propylene glycol alginate, optionally hydrogenated lecithins, optionally hydrogenated lysolecithins, lysophospholipids, phospholipids, alkylsulfate salts, fatty acid salts and/or sodium docusate.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Active Agent: (I) is selected from hydrophobic agents that are analgesics, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, anti-bacterial agents, anti-viral agents, anti-coagulants, anti-depressants, anti-diabetics, anti-epileptics, anti-fungal agents, anti-gout agents, anti-hypertensive agents, anti-malarials, anti-migraine agents, anti-muscarinic agents, anti-neoplastic agents, erectile dysfunction improvement agents, immunosuppressants, anti-protozoal agents, anti-thyroid agents, anxiolytic agents, sedatives, hypnotics, neuroleptics, D-Blockers, cardiac inotropic agents, corticosteroids, diuretics, anti-parkinsonian agents, gastro-intestinal agents, histamine receptor antagonists, keratolytics, lipidregulating agents, anti-anginal agents, COX-2 inhibitors,leucotriene inhibitors, macrolides, muscle relaxants, nutritional agents, opioid analgesics, protease inhibitors, sex hormones, stimulants, muscle relaxants, anti-osteoporosis agents,anti-obesity agents, cognition enhancers, anti-urinary incontinence agents, nutritional oils, anti-benign prostate hypertrophy agents, essential fatty acids and/or non-essential fatty acids. (I) is selected from acutretin, albendazole, albuterol, aminogluthemide, amiodarone, arniodipine, amphetamine, amphotericin B, atorvastatin, atovaquone, azithromycin, bactofen, beclomethsone, benezepril, benzonatate, betamethasone, bicalutanide, budesonide, bupropion, busulphan, butenafine, calcifediol, calciprotiene, calcitriol, camptothecan, candesartan, capsaicin, carbamezepine, carotenes, celecoxib,

cerivistatin, cetrizine, chlorpheniramine, cholecalciferol, cilostazol, cimetidine, cinnarizine, ciprofloxacin, cisapride, clarithromycin, clemastine, clormphene, clornipramine, clopidrogel, codeine, coenzyme Q10, cyclobenzaprine, cyclosporine, danazol, dantrolene, dexchlopheniramine, diclofenac, dicournarol, digoxin, dihydroepiandrosterone, dihydroergotamine, dihydrotachysterol, dirithromycin, donepezil, efavirenz, eposartan, ergocalciferol, ergotarnine, essential fatty acid sources, etodolac, etoposide, famotidine, fenofibrate, fentanyl, fexofenadine, finasteride, flucanazole, flurbiprofen, fluvastatin, fosphenytion, frovatriptan, furazolidone, gabapentin, gemfibrozil, glibenclamide, glipizide, glyburide, glymepride, griseofulvin, halofantrine,lbuprofen, irbesartan, irinotecan, isosorbide dinitrate, isotreinoin, itraconazole, ivermectin, ketoconazoie, ketorolac, lamotrigine, lanosprazole, leflunomide, lisinopril,loperamide, loratadine, lovastatin, L-thryroxine, lutein, lycopene, medroxyprogesterone,mefepristo ne, mefloquine, megesterol acetate, methadone, methoxsalen, metronidazole, metronidazole, miconazole, midazolam, miglitol, minoxidil, mitoxantrone, montelukast, nabumetone, nalbuphine, naratiptan, nelfinavir, nifedipine, nilsolidipine, nilutanide, nitrofurantoin, nizatidine, orneprazole, oprevelkin, osteradiol, oxaprozin, paclitaxel, paricalcitol, paroxetine, pentazocine, pioglitazone, pizofetin, pravastatin, prednisolone, probucol, progesterone, pseudo-ephedrine, pyridostigmine, rabeprazole, raloxifene, refocoxib, repaglinide, rifabutine, rifapentine, rimexolone, ritanovir, rizatriptan, rosigiltazone, saquinavir, sertraline, sibutramine, sildenafil citrate, simvastatin, sirolimus, spironolactone, sumatriptan, tacrine, tacrolimus, tamoxifen, tamsulosin, targretin,tazarotene, telmisartan, teniposide, terbinafine, terzosin, tetrahydrocannabinol, tiagabine,ticlidopine, tirofibran, tizanidine, topiramate, topotecan, toremifene, trarnadol, tretinoin, troglitazone, trovafloxacin, ubidecarenone, valsartan, venlafaxine, vertoporfin, vigabatrin, vitamin A, vitamin D, vitamin E, vitamin K, zafirlukast, zileuton, zolmitriphan, zolpidem and/or zopiclone. (I) may also be selected from acarbose, acylovir, acetylcysteine, acetylcholine chloride, alatrofloxacin, alendronate, alglucerase, amantadine hydrochloride, ambenomium, amifostine, amiloride hydrochloride, aminocaproic acid, amphotericin B, antihemophilic factor (human), antihemophilic factor (porcine), antihemophilic factor (recombinant), aprotinin, asparaginase, atenolol, atracurium besylate, atropine, azithromycin, aztreonam, BCG vaccine, bacitracin, becalermin, belladona, bepridil hydrochloride, bleomycin sulfate, calcitonin human, calcitonin salmon, carboplatin, capecitabine, capreomycin sulfate, cefamandole nafate, cefazolin sodium, cefepime hydrochloride, cefixime, cefonicid sodium, cefoperazone, cefotetan disodium, cefotoxime, cefoxitin sodium, ceftizoxime, ceftriaxone, cefuroxime axetil, cephalexin, cephapirin sodium, cholera vaccine, chrionic gonadotropin, cidofovir, cisplatin, cladribine, clidinium bromide, clindamycin and clindamycin derivatives, ciprofloxacin, clondronate, colistimethate sodium, colistin sulfate, cortocotropin, cosyntropin, cromalyn sodium, cytarabine, daltaperin sodium, danaproid, deforoxamine, denileukin diftitox, desmopressin, diatrizoate megluamine and diatrizoate sodium, dicyclomine, didanosine, dirithromycin, dopamine hydrochloride, domase alpha, doxacurium chloride, doxorubicin, editronate disodium, elanaprilat, enkephalin, enoxacin, enoxaprin sodium, ephedrine, epinephrine, epoetin alpha, erythromycin, esmol hydrochloride, factor IX, famiciclovir, fludarabine, fluoxetine, foscarnet sodium, ganciclovir, granulocyte colony stimulating factor, granulocyte-macrophage stimulating factor, growth hornone-recombinant human, growth hormone-bovine, gentamycin, glucagon, glycopyrolate, gonadotropin releasing hormone and synthetic analogs, GnRH, gonadorelin, grepafloxacin, hemophilus B **conjugate** vaccine, Hepatitis A virus vaccine inactivated, Hepatitis B virus vaccine inactivated, heparin sodium, indinavir sulfate-, influenza virus vaccine, interleukin-2, interleukin-3, insulin-human, insulin lispro, insulin procine, insulin NPH, insulin aspart, insulin glargine, insulin detemir, interferon alpha, interferon beta, ipratropium

bromide, isofosfamide, japanese encephalitis virus vaccine, lamivudine, leucovorin calcium, leuprolide acetate, levofloxacin, lincomycin and lincomycin derivatives, lobucavir, lomefloxacin, loracarbef, mannitol, measles virus vaccine, meningococcal vaccine, menotropins,mephenzolate bromide, mesalmine, methanamine, methotrexate, methscopolamine, metformin hydrochloride, metroprolol, mezocillin sodium, rnivacurium chloride, mumps, viral vaccine, nedocromil sodium, neostigmine bromide, neostigmine methyl sulfate, neutontin, norfloxacin, octreotide acetate, ofloxacin, olpadronate, oxytocin, pamidronate disodium, pancuronium bromide, paroxetine, pefloxacin, pentarnindine isethionate, pentostatin, pentoxifylllne, periciclovir, pentagastrin, phentolarnine mesylate, phenylalanine, physostigmine salicylate, plague vaccine, piperacillin sodium, platelet derived growth factor-human, pneumococcal vaccine polyvalent, poliovirus vaccine inactivated, pollovirus vaccine live (OPV), polymixin B sulfate, pralidoxine chloride, pramlintide, pregabalin, propofenone, propenthaline bromide, pyridostigmine bromide, rabies vaccine, residronate, ribavarin, rimantadine hydrochloride, rotavirus vaccine, salmetrol xinafoate, sincalide, small pox vaccine, solatol, somatostatin, sparfloxacin, spectinomycin, stavudine, streptokinase, streptozocin, suxamethoniurn chloride, tacrine hydrochloride, terbutaline sulfate, thiopeta, ticarcillin, tiludronate, timolol, tissue type plasminogen activator, TNFR:Fc, TNK-tPA, trandolapril, trimetrexate gluconate, trospectinomycin, trovafloxacin, tubocurarine chloride, tumor necrosis factor, typhoid vaccine live, urea, urokinase, vancomycin, valaciclovir, valsartan, varicella virus vaccine live, vasopressin and vasopressin derivatives, vecoronium bromide, vinblastin, vincristine, vinorelbine, vitamin B12 , warfarin sodium, yellow fever vaccine, zalcitabine, zanamavir, zolandronate, and/or zidovudine.

ABEX UPTX: 20010910

ADMINISTRATION - The composition is formulated for oral, nasal, ocular, urethral, buccal, transmucosal, vaginal, topical or rectal delivery (claimed). Dosage not given.

EXAMPLE - A composition was prepared containing (g): glyburide (1); PEG-4 stearate (33), glycerol monolaurate (17) and non-pareil seed (30/35 mesh) (80). The composition was formulated as coated beads.

L115 ANSWER 19 OF 21 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2001-182932 [18] WPIX
DNC C2001-054613
TI Novel amide of bile salt which is **conjugated** to a biologically active substance useful for improving and/or increasing bioavailability of biologically active substance when administered orally or parenterally.
DC B04
IN LUCAS, M L; MORRISON, J D; WHEELER, S
PA (UNIU) UNIV GLASGOW; (LUCA-I) LUCAS M L; (MORR-I) MORRISON J D; (WHEE-I) WHEELER S
CYC 95
PI WO 2001009163 A2 20010208 (200118)* EN 28 C07J000-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
GB 2355009 A 20010411 (200122) C07K017-00 <--
AU 2000061739 A 20010219 (200129) C07J000-00
EP 1228093 A2 20020807 (200259) EN C07K014-595 <--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
ADT WO 2001009163 A2 WO 2000-GB2903 20000728; GB 2355009 A GB 1999-17793 19990730; AU 2000061739 A AU 2000-61739 20000728; EP 1228093 A2 EP 2000-948177 20000728, WO 2000-GB2903 20000728

FDT AU 2000061739 A Based on WO 2001009163; EP 1228093 A2 Based on WO 2001009163

PRAI GB 1999-17793 19990730

IC ICM C07J000-00; **C07K014-595**; **C07K017-00**
ICS **A61K038-04**; A61K047-28; A61K047-48; **C07K014-47**; **C07K014-575**

AB WO 200109163 A UPAB: 20010402
NOVELTY - An amide of a bile acid/salt bonded by an amide bond to a peptide (I), is new.

DETAILED DESCRIPTION - An amide of a bile acid/salt bonded by an amide bond to a peptide of formula -X-Y (I), is new.

X = a peptide chain of at least four amino acids in length or comprise two or more cross-linked polypeptide chains; and

Y = OH, NH2, or a 1-6C ester group bonded to the terminal carboxy of the polypeptide chain.

INDEPENDENT CLAIMS are also included for:

(1) preparation of a pharmaceutical formulation involves bringing into association (I) and a carrier; and

(2) use of an amide of a bile acid/salt compound of formula (III) in the manufacture of a medicament suitable for parenteral administration.

R1-R5 = OH, H or 1-6C alkyl;

B' = -R6-CO-Z;

R6 = 2-6C alkylene; and

Z = a pharmaceutically active agent.

ACTIVITY - Anesthetic; tranquilizer; hypnotic; neuroleptic; antidepressant; anticonvulsant; antiparkinsonian; analgesic; neuroprotective; vasodilator; antianginal; cardiant; anticoagulant; antilipemic; antiinflammatory; antiulcer; bactericidal; virucidial; fungicidal; parasiticidal; antianemic.

MECHANISM OF ACTION - None given.

USE - (I) is useful for therapy and is useful in the manufacture of a medicament in a form suitable for oral administration.

ADVANTAGE - **Conjugation** of a pharmaceutically active substance to the bile acid via the carboxylic acid group of the bile acid results in improved uptake of the active substance into the blood stream when administered orally. The **conjugated** compound may also be administered parenterally at much lower doses than **unconjugated** form of the biologically active substance. The pharmacokinetics and/or bioavailability of a biologically active material are improved when a bile salt or acid-**conjugated** biologically active material is administered parenterally.

Experiments were carried out on male Wistar rats. After anesthetization the surgical procedures were carried out to allow incubation of the stomach at the pyloroduodenal junction after ligation of the esophagus to measure gastric acid secretion, cannulation of the terminal ileum and/or of the proximal jejunum distal to the ligament of Treitz for infusion of peptide hormones. Gastric acid secretion was measure by the following method. Gastrin tetrapeptide (G4) (Trp-Met-Asp-Phe amide) and cholate-Trp-Met-Asp-Phe amide **conjugate** (G4-CA), was used as the test substance. Experiments with gastrin tetrapeptide (G4) showed that biologically active G4 was not absorbed across the wall of the small intestine. In 6 experiments, ileal infusion of a large dose of G4 (2500 micro g kg-1 in 1.0 ml isotonic saline) actually resulted in a fall in the mean gastric acid level of 0.23 plus or minus 0.21 micro mol hr-1. Thus, it was demonstrated that G4 was not absorbed across the wall of the ileum. This lack of absorption of G4 was also confirmed for the upper jejunum. It was also to test whether G4-CA was absorbed from the small intestine: in this case, the relatively low dose of 600 micro g kg-1 G4-CA was injected intraileally. The first intravenous injection of G4-CA (15 micro g kg-1) caused a significant mean peak increase above baseline in total acidity of 0.64 plus or minus 0.26 micro mol 15 min-1 (P=0.017), while the second intravenous (i.v.) injection also caused significant increase of 0.72 plus or minus 0.26

micro mol 15 min-1 (P=0.003) of 17 rats, ileal administration of G4-CA (600 micro g kg-1) resulted in a significant mean increase in gastric acid secretion of 1.84 plus or minus 1.49 micro mol (P=0.045) over the 3 hour collection period. When the G4-CA was infused into the jejunum, no increase in gastric acid secretion occurred. Furthermore, when this jejunal infusion was then followed after 3 hours by ileal infusion of G4-CA, gastric acid secretion was strongly stimulated. In 5 rats, infusion of G4-CA (600 micro g kg-1 in 1.0 ml) into the jejunum caused a significant mean reduction in gastric acid levels. When G4-CA (600 micro g kg-1) was subsequently injected intra-ileally, the gastric acid levels were significantly increased by 1.63 plus or minus 0.31 micro mol. These results demonstrated the absorption of G4-CA with biological activity preserved. Furthermore, the absorption did not occur from the jejunum but was specific to the ileum: this indicated a requirement for bile salt facilitated transport. Experiments with gastrin decapeptide (G10) also showed that when G10-CA was infused intra-ileally on the same molar basis as G4-CA (1000 micro g kg-1 in 1.0 ml), there was considerable stimulation of gastric acid secretion. This confirmed that longer peptides were transportable across the wall of the ileum.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B01-D02; B04-B04H; B04-C01A; B04-C01G; B04-C02; B04-E01; B04-G01; B04-H06; B04-H07; B04-J01; B04-L01

TECH UPTX: 20010402

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Amide: The amide of a bile acid/salt is preferably a compound of formula (II).

R1-R5 = OH, H or 1-6C alkyl;

A = -R6-CO-X-Y;

R6 = 2-6C alkylene;

X = peptide of at least 4 amino acids long or comprises two or more cross-linked polypeptide chains; and

Y = OH, NH2 or 1-6C ester group bonded to the terminal carboxy of the polypeptide chain.

In the amide of a bile acid/salt, a peptide of 4-600 amino acids (preferably 4-200 amino acids) long is bound. The peptide is preferably insulin, secretin, gastrin, gastrin releasing peptide, glucagon, cholecysotokinin (CCK), gastric inhibitory peptide (known as glucose' insulinotropic peptide (GIP)), parathyroid hormone, thyrotropin-releasing hormone, gonadotropin-releasing hormone (also known as lutenizing hormone releasing hormone (LHRH)), corticotropin-releasing hormone, somatostatin, adrencorticotropic hormone (ACTH), renin, angiotensin I, angiotensin II, atrial natriuretic hormone (ANH), somatomedins, calcitonin, hemoglobin, cytochrome C, horseradish peroxidase, aprotinin, mushroom tyrosinase, erythropoietin, somatotropin (growth hormone), growth hormone releasing hormone, galanin, urokinase, Factor IX (also known as Christmas factor), tissue plasminogen activator, antibodies, superoxide dismutase, catalase, peroxidase, ferritin, interferon, Factor VIII, soybean trypsin inhibitor, GLP1, blood coagulation factors, somatostatin, antidiruetic hormone (ADH), oxytocin, polysaccharides, hirudin, and glycoproteins, such as follicle stimulating hormone (FSH), lutenizing hormone (LH) inhibin, chorionic gonadotropin (FSH), and thyroid stimulating hormone (TSH), and analogs and fragments of all these, or mixtures of one or more of these. The bile salt is preferably mono-, di- or tri-hydroxylated, contains a 3alpha-hydroxyl group, is an **amphiphilic** polyhydric sterol bearing carboxyl groups as part of the primary side chain and is derivatized or underivatized. The underivatized bile salt is preferably cholate, deoxycholate, chenodeoxycholate and urosodeoxycholate. The derivatized bile salt is taurocholate, taurodeoxycholate, taurourosodeoxycholate, glycoursodeoxycholate, glycochenodeoxycholate, taurolithocholate and glycolithocholate. Preferably, the somatomedins are IGF1 or IGF2 and the antibody is IgM, IgA, IgG, IgD or IgE.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: (II) is formulated to be administered orally and is thus encapsulated to prevent formulation degradation in the stomach. In (III), Z is bound to the bile salt by acid/salt by an amide linkage. The pharmaceutical agent Z is a polypeptide and glycoprotein, polysaccharide, **oligonucleotide** /polynucleotide, anesthetic, anxiolytic, hypnotic, neuroleptic, antidepressant, anti-epileptic, anti-Parkinsonian drug, opioid analgesics, neuropeptide transmitter, neuropeptide transmitter antagonist, muscarinic agonist, anticholinesterase, muscarinic antagonist, nicotinic antagonist, direct sympathomimetic, indirect sympathomimetic, adrenergic blocking drug, adrenoreceptor antagonist, vasodilators, anti-angina drug, cardiotonic drug, anti-dysrhythmic drug, anticoagulant, plasma lipid lowering drug, anti-anemia drug, antiinflammatory drug, diuretics, histamine antagonist, anti-peptic ulcer drug, anti-gut motility disorder drug, chemotherapy drug, anti-bacterial drug, anti-viral drug, anti-fungal drug and anti-parasite drug.

ABEX UPTX: 20010402

ADMINISTRATION - The peptide **conjugates** are administered preferably orally, and encapsulated to prevent formulation degradation in the stomach (claimed). Dosages range from 0.01-120 (preferably 0.1-50) mg/kg body weight.

L115 ANSWER 20 OF 21 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2001-102601 [11] WPIX
DNC C2001-029994
TI New drug-**oligomer conjugates** facilitate oral delivery of e.g. insulin, and can delay the onset of activity or extend the duration of activity of drug in the bloodstream.
DC A96 B04 C03
IN EKWURIBE, N; RAJAGOPALAN, J; RAMASWAMY, M; EKWURIBE, N N; RAJAGOPALAN, J S
PA (PROT-N) PROTEIN DELIVERY INC; (NOBE-N) NOBEX CORP; (NOBE-N) NOBEX INC
CYC 95
PI WO 2000078302 A1 20001228 (200111)* EN 69 A61K031-075
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000057500 A 20010109 (200122)
US 6309633 B1 20011030 (200172) A61K009-107
NO 2001006143 A 20020218 (200228) A61K000-00
BR 2000011772 A 20020402 (200231) A61K031-075
EP 1196157 A1 20020417 (200233) EN A61K031-075
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
CZ 2001004597 A3 20020515 (200241) A61K031-075
KR 2002012278 A 20020215 (200257) A61K047-48
CN 1368877 A 20020911 (200282) A61K031-075
JP 2003502364 W 20030121 (200308) 68 A61K047-48
HU 2002003745 A1 20030428 (200337) A61K031-075
ZA 2001010099 A 20030528 (200341) 80 A61K000-00
MX 2002000054 A1 20030701 (200366) A61K031-075
NZ 516109 A 20040430 (200431) A61K031-075
ADT WO 2000078302 A1 WO 2000-US16879 20000619; AU 2000057500 A AU 2000-57500 20000619; US 6309633 B1 US 1999-336548 19990619; NO 2001006143 A WO 2000-US16879 20000619, NO 2001-6143 20011217; BR 2000011772 A BR 2000-11772 20000619, WO 2000-US16879 20000619; EP 1196157 A1 EP 2000-942956 20000619, WO 2000-US16879 20000619; CZ 2001004597 A3 WO 2000-US16879 20000619, CZ 2001-4597 20000619; KR 2002012278 A KR 2001-716204 20011217; CN 1368877 A CN 2000-811540 20000619; JP 2003502364 W WO 2000-US16879 20000619, JP 2001-504366 20000619; HU 2002003745 A1 WO 2000-US16879 20000619, HU 2002-3745 20000619; ZA 2001010099 A ZA

2001-10099 20011207; MX 2002000054 A1 WO 2000-US16879 20000619, MX 2002-54 20011219; NZ 516109 A NZ 2000-516109 20000619, WO 2000-US16879 20000619

FDT AU 2000057500 A Based on WO 2000078302; BR 2000011772 A Based on WO 2000078302; EP 1196157 A1 Based on WO 2000078302; CZ 2001004597 A3 Based on WO 2000078302; JP 2003502364 W Based on WO 2000078302; HU 2002003745 A1 Based on WO 2000078302; MX 2002000054 A1 Based on WO 2000078302; NZ 516109 A Based on WO 2000078302

PRAI US 1999-336548 19990619

IC ICM A61K000-00; A61K009-107; A61K031-075; A61K047-48

ICS A61K031-13; A61K031-16; A61K031-21; A61K031-325; **A61K038-00** ; **A61K038-02**; **A61K038-17**; **A61K038-22**; **A61K038-28**; A61K039-385; A61P003-10; **C07K001-113**

AB WO 200078302 A UPAB: 20010224

NOVELTY - Drug-**oligomer conjugates** (I) which include a **hydrophilic** component and a **lipophilic** component liked by a hydrolyzable bond, are new.

DETAILED DESCRIPTION - Drug-**oligomer conjugates** (I), (X), (XI), (XII) and (XIII), which include a **hydrophilic** component and a **lipophilic** component liked by a hydrolyzable bond, are new.

D = therapeutic drug moiety;

H, H' = **hydrophilic** moieties selected from straight or branched polyethylene glycol (PEG) polymers which have 2-130 ethylene glycol subunits and sugars;

L = **lipophilic** moiety selected from 2-24C alkyl groups, cholesterol and fatty acids;

m + n + p = at least one, but does not exceed the total number of covalent bonding sites on D for the substituents H', L and H-L;

o (defined in the disclosure) = 1 to the maximum number of covalent binding sites on H; and

L' (defined in the disclosure) = L.

INDEPENDENT CLAIMS are included for:

(1) drug-**oligomer conjugate** of formula (XI), in which the S-L and/or S-H bond is hydrolyzable;

(2) drug-**oligomer conjugates** of formula (XII), in which the S-H and/or S-H' bond is hydrolyzable;

(3) drug-**oligomer conjugates** of formula (XIII), in which the H-H' bond is hydrolyzable;

(4) drug-**oligomer conjugates** of formula (X), in which the H-H' bond is hydrolyzable; and

(5) method of providing to a subject an active drug-PEG **conjugate** of formula (X), in which the H-H' bond is hydrolyzable and the H'L bond is not hydrolyzable, D is insulin or a derivative, where (X) has enhanced activity compared to **unconjugated** insulin.

S = spacer group selected from sugars, carbohydrates and glycerol;

n = 1 to the maximum number of covalent binding sites at which S can be attached to H;

o = 1 to the maximum number of covalent binding sites at which L can be attached to S;

p = 1 to the maximum number of covalent binding sites at which ((H-Sn)Lo)p can be attached to D; and

q = 1 to the maximum number of covalent binding sites at which H' can be attached to S.

ACTIVITY - Antidiabetic; virucide; antibacterial.

MECHANISM OF ACTION - None given.

USE - The new **conjugates** can be used in treatment or prevention of any disorders which can be treated by the therapeutic drug D, including bacterial and viral infections. Drug D is preferably insulin, useful in treatment of diabetes.

ADVANTAGE - The new **conjugates** contain **hydrophilic** components, **lipophilic** components and drug components. These components are variously linked such that, upon hydrolysis of hydrolyzable bonds in the **conjugates**, an active drug-**hydrophile**

conjugate remains. The **oligomers** are very suitable for oral delivery, while extending the onset of activity of drug-**oligomer conjugate** in the blood stream. The **lipophilic** component is preferably selected such that the drug component is inactive until the hydrolyzable bond is hydrolysed. **Amphiphilic** modification of insulin improves its **lipophilicity** and stabilizes it against enzymatic degradation while improving its membrane permeability.
Dwg.0/3
FS CPI
FA AB; GI; DCN
MC CPI: A10-E01; A12-V01; B01-D02; B04-C03C; B04-D01; B04-J03A; B04-N04; B09-D01; B14-A01; B14-A02; B14-F09; C01-D02; C04-C03C; C04-D01; C04-J03A; C04-N04; C09-D01; C14-A01; C14-A02; C14-F09
TECH UPTX: 20010224
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred materials: In (I), the D-H and D-H' bonds, when present are non-hydrolyzable. The D-L' bond, when present, is non-hydrolyzable. The D-H and D-H' bonds are especially carbamate, amide or secondary amine bonds. The H-L bond and D-L' bond are especially ester or carbonate bonds. In all the new **conjugates**, D is especially a biologically active polypeptide (especially insulin) or an antigen from an organism associated with a disease state. The polyethylene glycol component typically contains 2-7 ethylene glycol units, especially 3 ethylene glycol units.

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Hydrolyzable **oligomers** can be synthesized e.g. by coupling fatty acid chlorides with an equivalent of PEG. Non-hydrolyzable **oligomers** can be synthesized, e.g., by coupling an alkyl bromide with the monosodium salt of an appropriate PEG. The **oligomers** can be activated with N-hydroxysuccinimide and coupled to insulin (or some other drug).
ABEX UPTX: 20010224
ADMINISTRATION - Administration of the **conjugates** is by any conventional method e.g. parenteral, topical, sublingual, mucosal, nasal or transdermal, preferably oral. The drug-**oligomer conjugates** can be administered in association with an emulsion or microemulsion. Typical doses of insulin **conjugates** are 0.1-5 (especially 0.2-0.3) mg/kg.

EXAMPLE - Insulin (1.503 g) was added to a round bottom flask equipped with a stirrer bar. Dimethyl sulfoxide (DMSO; 5 ml) was added and the mixture was stirred until the insulin dissolved. Triethylamine (2.08 mmol) was added and the mixture was stirred for 10 minutes. Activated oleate triethylene glycol was added in a minimum amount of DMSO (2 ml). The mixture was stirred for 3 hours at room temperature. The **conjugate** was purified using preparative HPLC.

L115 ANSWER 21 OF 21 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2000-256190 [22] WPIX
DNC C2000-078134
TI **Amphiphilic** drug-**oligomer conjugate** for delivery of therapeutic agents, used to treat central nervous system disorders, or diagnostic agents across the blood brain barrier.
DC A96 B04 B05
IN ANDERSON, W R; ANSARI, A M; EKWURIBE, N N; PRICE, C H; RADHAKRISHNAN, B; AUSARI, A M; ANDERSON, W; RHADAKRISHNAN, B
PA (PROT-N) PROTEIN DELIVERY INC; (NOBE-N) NOBEX CORP; (NOBE-N) NOBEX INC; (ANDE-I) ANDERSON W R; (ANSA-I) ANSARI A M; (EKWU-I) EKWURIBE N N; (PRIC-I) PRICE C H; (RADH-I) RADHAKRISHNAN B
CYC 83
PI WO 2000009073 A2 20000224 (200022)* EN 75 A61K000-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW

W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW

AU 9956726	A	20000306 (200030)			A61K031-705	
EP 1105142	A2	20010613 (200134)	EN		A61K031-705	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI						
BR 9914280	A	20011113 (200201)			A61K031-704	
					A61K047-48	
KR 2001072472	A	20010731 (200209)			A61K031-704	
CN 1323213	A	20011121 (200218)			A61K047-48	
JP 2002522463	W	20020723 (200263)		78	A61K000-00000	
MX 2001001694	A1	20020501 (200368)			A61K031-56	<--
US 6703381	B1	20040309 (200418)			A61K038-23	<--
US 2004102381	A1	20040527 (200435)			A61K031-56	
US 2004110735	A1	20040610 (200438)				

ADT WO 2000009073 A2 WO 1999-US18248 19990812; AU 9956726 A AU 1999-56726 19990812; EP 1105142 A2 EP 1999-943676 19990812, WO 1999-US18248 19990812; BR 9914280 A BR 1999-14280 19990812, WO 1999-US18248 19990812; KR 2001072472 A KR 2001-701888 20010213; CN 1323213 A CN 1999-812133 19990812; JP 2002522463 W WO 1999-US18248 19990812, JP 2000-564577 19990812; MX 2001001694 A1 WO 1999-US18248 19990812, MX 2001-1694 20010213; US 6703381 B1 US 1998-134803 19980814; US 2004102381 A1 Div ex US 1998-134803 19980814, US 2003-716578 20031119; US 2004110735 A1 Div ex US 1998-134803 19980814, US 2003-716975 20031119

FDT AU 9956726 A Based on WO 2000009073; EP 1105142 A2 Based on WO 2000009073; BR 9914280 A Based on WO 2000009073; JP 2002522463 W Based on WO 2000009073; MX 2001001694 A1 Based on WO 2000009073; US 2004102381 A1 Div ex US 6703381; US 2004110735 A1 Div ex US 6703381

PRAI US 1998-134803 19980814; US 2003-716578 20031119; US 2003-716975 20031119

IC ICM A61K000-00; A61K000-00000; A61K031-56; A61K031-704; A61K031-705; **A61K038-23**; A61K047-48

ICS **A61K038-00**; **A61K038-04**; **A61K038-11**; **A61K038-21**; **A61K038-22**; **A61K038-26**; **A61K038-27**; **A61K038-33**; **A61K038-36**; **A61K038-42**; **A61K038-46**; **A61K038-48**; **A61K039-395**; A61K045-00; A61P005-02; A61P005-10; A61P005-14; A61P005-18; A61P029-00; A61P043-00; **C07K014-70**; **C07K017-00**

AB WO 200009073 A UPAB: 20000508

NOVELTY - **Amphiphilic** drug-**oligomer conjugate** comprising a therapeutic compound **conjugated** to an **oligomer** comprising a **lipophilic** moiety coupled to a **hydrophilic** moiety, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an **amphiphilic oligomer**-enkephalin **conjugate** selected from the group consisting of DHA Met-enkephalin-Lys, linoleic Met-enkephalin-Lys, cetyl Met-enkephalin-Lys, cholesterol Met-enkephalin-Lys, palmitate-teg Met-enkephalin-Lys, and di-palmitate-teg Met-enkephalin-Lys;

(2) an **amphiphilic oligomer**-enkephalin **conjugate** where the **oligomer** comprises a **lipophile** coupled to a **hydrophile** by a hydrolyzable bond, the **conjugate** being DHA Met-enkephalin-Lys, linoleic Met-enkephalin-Lys or cetyl Met-enkephalin-Lys;

(3) an **amphiphilic oligomer**-enkephalin **conjugate** where the **oligomer** comprises a **lipophile** coupled to a **hydrophile** by a non-hydrolyzable bond, the **conjugate** being cholesterol Met-enkepahlin-Lys, palmitate-teg Met-enkephalin-Lys or di-palmitate-teg Met-enkephalin-Lys;

(4) a method for activating a receptor comprising bringing the

receptor into contact with the novel **conjugate**;

(5) a method for delivering a therapeutic compound across the blood-brain barrier comprising administering the novel **conjugate**;

(6) a method for inducing analgesia in a subject, comprising administering the novel **conjugate**; and

(7) a method for altering the binding affinity of a peptide or protein to its receptor, comprising **conjugating** the peptide to the novel **conjugate**.

ACTIVITY - Cerebroprotective.

MECHANISM OF ACTION - None given.

USE - The **conjugates** are capable of traversing the blood-brain barrier and so delivering therapeutic agents used in the treatment of disease states associated with the central nervous system (CNS) or for delivering diagnostic agents across the blood brain barrier.

ADVANTAGE - The **conjugates** are stable in the bloodstream and resist degradation by the enzymes of the blood brain barrier and in the CNS. The **conjugates** readily cross the blood brain barrier.

Dwg.0/10

FS CPI

FA AB; DCN

MC CPI: A12-V01; B01-D02; B04-C01B; B12-K04; B14-J01

TECH UPTX: 20000508

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Compound: The therapeutic compound is a peptide or protein comprising enkephalin, adrenocorticotropic hormone, adenosine deaminase ribonuclease, alkaline phosphatase, angiotensin, antibodies, arginase, arginine deaminase, asparaginase, caerulein, calcitonin, chemotrypsin, cholecystokinin, clotting factors, dynorphins, endorphins, enkephalins, erythropoietin, gastrin-releasing peptide, glucagon, hemoglobin, hypothalmic releasing factors, interferon, katacalcin, motilin, neuropeptide Y, neurotensin, non-naturally occurring opioids, oxytosin, papain, parathyroid hormone, peptides prolactin, soluble CD-4, somatomedin, somatostatin, somatotropin, superoxide dismutase, thyroid stimulating hormone, tissue plasminogen activator, trypsin, vasopressin and analogs or active fragments of them, as well as other enzymes, hormones, proteins, polypeptides, enzyme-protein **conjugates**, antibody-hapten **conjugates**, viral epitopes etc. Particularly preferred are opioid receptor agonists, antagonists or partial agonists/antagonists and especially (met5)enkephalin. Other therapeutic agents include nucleosides, nucleotides, antiviral agents, antineoplastic agents, antibodies, and prodrugs, precursors, derivatives and intermediates of them.

Preferred **Oligomer**: The **oligomer** comprises at least 1 **lipophilic** and 1 **hydrophilic** moiety and the nature of the respective moieties is selected so as to impart an **amphiphilic** nature to the resulting **conjugate**. The **lipophilic** moiety is optionally coupled to the **hydrophilic** moiety by a hydrolyzable or a non-hydrolyzable bond. The bond is preferably an amide, carbamate, carbonate or ester bond. The **lipophilic** moiety of the **oligomer** is preferably selected from a 4-26 (preferably 14-22) C fatty acid, 1-26 C alkyl, cholesterol or adamantane. The **hydrophilic** moiety is preferably a small segment of polyethylene glycol (PEG), preferably 1-7 PEG units or a sugar which is an amino or non-amino sugar.

Preferred **Conjugates**: The **conjugate** may exhibit activity with or without cleavage of the therapeutic compound from the **oligomer**. The **oligomer** moiety is typically coupled to the drug moiety by a bond selected form an amide, carbamate, carbonate or ester bond.

Preferred method: The receptor is a G-protein coupled receptor or an opiod receptor, selected from delta, mu and kappa receptors.

Preparation: In the synthesis of **oligomers** in which the portions are connected by ether linkages, the PEG is protected dissolved in an

inert solvent and treated with NaH. Bromo or tosylate derivative of the **lipophilic** portion is dissolved in inert solvent and added to the solution of the protected PEG. The product is then deprotected and purified. In the synthesis of **oligomers** where the portions are connected in ether bonds and the terminal ends in carboxylic acid moiety, it is desirable to protect the carboxylic group. PEG having free OH group at one end and COOH group at the other end is selected. The protected PEG is treated with Nah, Bromo or tosylate derivatives of the **lipophilic** portion is added to the solution of the protected PEG. The product is treated with a solution of NaOH to liberate the free acid, the desired product is then extracted and purified. This group of acidic **oligomers** can be coupled to peptide drugs by first reacting the carboxylic group with N-hydroxysuccinimide to form an easily cleavable group. A solution of the activated **oligomers** is treated with the desired peptide drug.

TECHNOLOGY FOCUS - POLYMERS - Preferred **conjugate**: An **amphiphilic** drug-**oligomer conjugate** comprising a therapeutic reagent **conjugated** to an **oligomer** where the **oligomer** comprises a **lipophilic** moiety coupled to a **hydrophilic** moiety. The therapeutic reagent is preferably a peptide or a protein. The **oligomer** comprises a **lipophilic** moiety which is selected from fatty acids, 1-26C alkyl, cholesterol and adamantane and the **hydrophilic** moiety is selected from sugars and small polyethylene glycol segments preferably comprising 1-7 PEG units

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SPECIFIC COMPOUNDS - The **oligomers** are preferably compounds (1)-(7): CH3(CH2)n(OC2H4)mOH where n is 3-25 and m is 1-7 (1); CH3(CH2)n(OC2H4)mOCH2CO2H where n is 3-25 and m is 1-6 (2); CH3(CH2)nCX(OC2H4)mOH where n is 3-25, m is 1-7 and X is O (3); R-(OC2H4)mCH2CO2H where m is 0-5 and R is cholesterol or adamantane (4); R-OCO(C2H4O)mCH2CO2H where m is 0-5 (5); CH3(CH2-CH=CH)6(CH2)2CH2(OC2H4)mOH where m is 0-7 (6); CH3(CH2-CH=CH)6(CH2)2CX(OC2H4)mOH where m is 1-7 and X is N or O (7).

ADMINISTRATION - Administration may be intradermal, intranuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural or oral. The dosage for enkephalin **conjugates** for analgesia may generally be in the range 1-20mg/kg, preferably 5-7 mg/kg.

EXAMPLE - To a stirring solution of met-enkephalin (0.13g) in 5ml of N,N, Dimethylformamide (DMF)-DCM (dichloromethane) (2:1) was added triethylamine (25 microliters). The mixture was cooled to 10degreesC and a solution of palmityl-teg-nsu or cetyl-teg-nsu dissolved in 1ml of DCM was added in one portion. The mixture was stirred for 2 hours at 10degreesC. The solvent was removed under reduced pressure and the residue was redissolved in dry ethyl acetate. After evaporation of the solvent, 0.31g of **conjugated** enkephalin was obtained. High performance liquid chromatography (HPLC) showed mono and **diconjugation** in the ratio 3:1.

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